Polypharmacy in older adults
– prevalence, risk factors, and associations with mortality – and the role of diabetes

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Student declaration

I, Yun-Ting Huang, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature: Date: 9th Aug. 2021

Abstract

Polypharmacy is common in ageing populations, but its impact on older adults' health and the role of diabetes are uncertain. This PhD aimed to better understand the prevalence and risk factors of polypharmacy and its associations with mortality, and to explore the role of diabetes in those relationships. Using data from the English Longitudinal Study of Ageing (2004–05 to 2012–13), this work comprised four studies.

The first investigated the prevalence and risk factors of undiagnosed diabetes. The prevalence of diagnosed (7.7% and 11.5%) and undiagnosed (2.4% and 3.4%) diabetes increased between 2004 and 2012. However, men aged 50–74 reported a stable prevalence of undiagnosed diabetes and improved awareness.

The second examined the prevalence and risk factors of polypharmacy according to diabetes status (diagnosed and undiagnosed). Older adults with diabetes had a higher prevalence of polypharmacy (41.1% versus 14.8%) and heightened polypharmacy (5.8% versus 1.7%) compared with those without diabetes, even excluding antihyperglycemic drugs. People with diabetes who were men and obese were more likely to show polypharmacy and heightened polypharmacy.

The third investigated associations between different levels of polypharmacy and all-cause and cause-specific mortality over six years. Polypharmacy and heightened polypharmacy showed dose-response relationships with all-cause (hazard ratio (HR) 1.51, 2.29) and cardiovascular disease (CVD) (subdistribution hazard ratio (SHR) 2.45, 3.67) mortality. Diabetes was a confounder in this relationship and independently related to all-cause mortality.

The fourth explored associations between high-risk medications and all-cause and cause-specific mortality among older adults with polypharmacy. Older adults with

polypharmacy who took mental health drugs, opioids and muscle relaxants were at higher risk of all-cause (HR 1.55) and CVD (SHR 2.11) mortality.

These findings highlight the importance of greater awareness of polypharmacy among older adults in England, especially those on specific high-risk medications, and special care for older people with diabetes.

Impact statement

There are several ways in which the discoveries and insights presented in this thesis might be impactful:

1. Clinical practice: this PhD research highlights the importance of greater awareness of polypharmacy (including heightened polypharmacy) among community-dwelling older adults in England, and it provides evidence to improve strategies for polypharmacy management. In addition to heightened polypharmacy and opioids, which are emphasised in the current guidance, older adults with polypharmacy – especially those on mental health medications and muscle relaxants – should also be included in medication reviews, which are regarded as a standard method of medication optimisation. The findings from this PhD can thus contribute to the improvement of current guidelines on polypharmacy management. This work also highlights the importance of diabetes, either in the development of polypharmacy or in adverse outcomes. Older adults with diabetes should therefore be given patient-centred healthcare that takes account of multimorbidity and polypharmacy concurrently. Additionally, the increasing prevalence observed over time of undiagnosed diabetes suggests that adults aged 75 and older may need regular monitoring of blood sugar levels to help early diagnosis, apart from those aged 40−74, who are targeted in NHS Health Checks.
2. Dissemination of research findings: three of my studies have been published in peer-reviewed scientific journals. The manuscript of my last study is almost finished and will be submitted to journals shortly. Moreover, I have presented

my research to specialists and non-specialists at four international and multidisciplinary conferences.

3. Future research: this PhD work establishes a rigorous definition of polypharmacy as well as a comprehensive adjustment of comorbidities in a population-based observational study of polypharmacy. This is a good reference for future studies. Findings from this work not only fill gaps in the literature but also shine a light on potential future research. Such research may investigate:
   - ❖ changes in polypharmacy and high-risk medications, and the role of diabetes in these changes
   - ❖ whether persistent polypharmacy (more than one measurement) better predicts mortality
   - ❖ trajectories of depressive symptoms and cognitive function, according to polypharmacy and diabetes status

Publications and presentations

This PhD work has resulted in four articles for peer-reviewed journals and four presentations at multidisciplinary international conferences. All the information is listed below.

Publications

Huang YT, Steptoe A, Wei L, Zaninotto P. The impact of high-risk medications on mortality risk among older adults with polypharmacy: evidence from the English Longitudinal Study of Ageing. BMC Medicine. 2021 19:321. doi: 10.1186/s12916-021-02192-1.

Huang YT, Steptoe A, Wei L, Zaninotto P. Dose-response relationships between polypharmacy and all-cause and cause-specific mortality among older people. Journals of Gerontology: Series A. 2021 Jun 3:glab155. doi: 10.1093/gerona/glab155. Epub ahead of print.

Huang YT, Steptoe A, Wei L, Zaninotto P. Polypharmacy difference between older people with and without diabetes: evidence from the English longitudinal study of ageing. Diabetes Res Clin Pract. 2021 Apr 30;176:108842. doi: 10.1016/j.diabres.2021.108842. Epub ahead of print.

Huang YT, Steptoe A, Zaninotto P. Prevalence of undiagnosed diabetes in 2004 and 2012: evidence from the English Longitudinal Study of Aging. Journals of Gerontology: Series A, 2021 Apr 30;76(5):922-928. doi: 10.1093/gerona/glaa179.

Presentations

Huang YT, Steptoe A, Wei L, Zaninotto P. (Sept 2021, oral) 'The impact of high-risk medications on mortality risk among older adults with polypharmacy in England'. Society for Social Medicine Annual Scientific Virtual Meeting, online.

Huang YT, Steptoe A, Wei L, Zaninotto P. (Sept 2020) 'Polypharmacy as a risk factor for all-cause mortality among older people in England'. ISPE 36th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, online.

Huang YT, Steptoe A, Wei L, Zaninotto P. (Sept 2019, oral) 'The prevalence and risk factors of polypharmacy among diabetic people: evidence from the English Longitudinal Study of Ageing (ELSA)'. Society for Social Medicine & Population Health Annual Scientific Meeting, Cork, Ireland.

Huang YT, Steptoe A., Zaninotto P. (Oct 2018) 'Trends in the prevalence of undiagnosed diabetes in English Longitudinal Study of Ageing (ELSA): 2004 to 2012'. ELSA Wave 8 Report Launch, London, UK.

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List of abbreviations

A & E: Accident and emergency

ACEI: Angiotensin-converting-enzyme inhibitor

ADA: American Diabetes Association

ADLs: Activities of daily living

ARB: Angiotensin II receptor blocker

BMI: Body mass index

BNF: British National Formulary

BZD: Benzodiazepine

CCB: Calcium channel blocker

CES-D: Centre for Epidemiological Studies Depression Scale

CHD: Coronary heart disease

CI: Confidence interval

CIF: Cumulative incidence function

CNS: Central nervous system

COPD: Chronic obstructive pulmonary disease

CVD: Cardiovascular disease

DBP: Diastolic blood pressure

DPP-4: Dipeptidyl peptidase-4

ELSA: English Longitudinal Study of Ageing

GLP-1: Glucagon-like peptide-1

GP: General practitioner

HbA1c: Glycated haemoglobin

HR: Hazard ratio

IADLs: Instrumental activities of daily living

IQR: Interquartile range

MUR: Medicines use review

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

NSAID: Non-steroidal anti-inflammatory drug

NS-SEC: National statistics socio-economic classification

OR: Odds ratio

OTC: Over-the-counter

PIM: Potentially inappropriate medication

PIP: Potentially inappropriate prescription

RAAS: Renin-angiotensin-aldosterone system

RRR: Relative risk ratio

SBP: Systolic blood pressure

SD: Standard deviation

SGLT-2: Sodium-glucose cotransporter-2

SHR: Subdistribution hazard ratio

SNRI: Serotonin and norepinephrine reuptake inhibitor

SSRI: Selective serotonin reuptake inhibitor

START: Screening tool to alert to right treatment

STOPP: Screening tool of older people’s prescriptions

SU: Sulphonylurea

TCA: Tricyclic antidepressant

TILDA: Irish Longitudinal Study on Ageing

TZD: Thiazolidinedione

WHO: World Health Organisation

Chapter 1. Literature review on polypharmacy

This chapter will start with a brief introduction to the issues of ageing and multimorbidity and then focus on polypharmacy. First I will review the definitions of polypharmacy, then I will move on to polypharmacy research, and lastly I will discuss the role of diabetes in polypharmacy. The gaps in current research and the aims of this PhD research are reported at the end of this chapter.

1.1 Introduction

'Polypharmacy' is a term widely used to describe the concomitant use of multiple medications. Such use is a legitimate response to the presence of multimorbidity that requires multiple drugs or regimens based on guideline recommendations. Older adults inevitably have reduced physical function and activity and therefore are more likely to develop multimorbidity and polypharmacy. Since both ageing and multimorbidity play a fundamental role in the development of polypharmacy, they will be discussed before I begin the literature review on polypharmacy.

1.1.1 Ageing population

With the progress of technology and medical science in the 21st century, human life expectancy is higher than ever before. In 2016, the average life expectancy at birth among the global population was 72 years; in the UK, the average life expectancy at birth for males and females was 80 and 83 years respectively (World Health Organisation (WHO) 2021). Longer life expectancy inevitably results in an increasing proportion of older people worldwide. According to the WHO, it is estimated that the

proportion of people aged 60 and over will nearly double globally from 12% in 2015 to 22% in 2050 (WHO 2018). The population in the UK is also getting older. In 2016, 18% of the UK population were aged 65 and over, and 2.4% were aged 85 and over; the percentage of people aged 65 and over is projected to reach 24.7% in 2046 (Randall 2017).

Vulnerability in ageing populations

Older adults appear to be vulnerable in terms of physical function, social support, and treatment complexity. Older people's unique characteristics contribute to difficulties in disease management, and therefore they need to be treated differently from the younger population. First, physical function in older people is different from that of younger adults, including body composition and hepatic and renal functions. Older people have an increasing ratio between fat and lean body mass, which accompanies the ageing process (Prentice and Jebb 2001), and this would lead to age-related changes in drug distribution. Drug distribution is highly related to the lipid solubility of each medication. The change in body composition therefore affects drug distribution and subsequently influences drug efficacy and drug elimination. Older adults also show declines in hepatic and renal function, which are the main pathways to metabolise and eliminate drugs from the human body (Wojtczak, Kasznicki, and Drzewoski 2017). Alterations in body composition and hepatic and renal function lead to changed pharmacokinetics, resulting in the unpredictable elimination half-life of medications. Thus, older adults may be exposed to high risks of adverse effects, such as the risk of falls with antihypertensives, or the risk of delirium with opioids (Davies and O'Mahony 2015). Second, older people are rarely followed up in pharmaceutical

clinical trials for new medications, because older people with multimorbidity are usually excluded from randomised controlled trials (Wojtczak, Kasznicki, and Drzewoski 2017). Accordingly, information on the efficacy and adverse effects of particular drugs among older adults is insufficient in clinical practice. Most clinical treatment guidelines tend to target individuals with a specific disease (e.g. younger adults) rather than people with complex comorbidities (e.g. older adults), contributing to the difficulty and complexity of disease management for older people. Third, older age is usually accompanied by more symptomatic treatments prescribed by physicians (Wojtczak, Kasznicki, and Drzewoski 2017). Long-term symptoms such as constipation, vertigo, and insomnia are common among older people, and they are probably related to frailty and reduced physical activity over the ageing process. Nevertheless, the detailed diagnoses and investigations that lie behind a specific symptomatic treatment might not be recorded by physicians, which may affect the overall treatment and may harm older adults' health in the long run (Wojtczak, Kasznicki, and Drzewoski 2017). Fourth, multimorbidity in older people results in multiple consultations with different specialists. Different specialists may prescribe duplicate medications or the same ingredient in different formulations, due either to a lack of medication review or to a lack of awareness among patients (Wojtczak, Kasznicki, and Drzewoski 2017). Lastly, a decline in cognition accompanies the normal ageing process, which may influence older adults' attention, memory, executive cognitive function, language, and visuospatial abilities (Murman 2015). Reduced cognitive abilities in older people may contribute to polypharmacy through their unawareness of the types of medication they take, their inability to describe or interpret symptoms, or repeated prescriptions from different specialist clinics. Also, impaired cognitive function may lead to non-adherence to treatments and subsequently damage disease management. To

summarise, features ranging from physiological changes to clinical settings distinguish older adults from the general adult population and complicate disease management for older people.

1.1.2 Multimorbidity

Multimorbidity, defined as the coexistence of two or more chronic conditions by the WHO, has become an urgent issue in terms of patient safety, health inequality, and healthcare expenditure (Geneva: WHO 2016). The prevalence of multimorbidity has been rising over recent decades, depending on the number of conditions included (Xu, Mishra, and Jones 2017; Geneva: WHO 2016). The prevalence of multimorbidity essentially increases with age and is nearly 100% among older people (Xu, Mishra, and Jones 2017). Relevant research on multimorbidity has intensively studied its definitions, patterns, risk factors, and interventions (Prados-Torres et al. 2014; Xu, Mishra, and Jones 2017; Hernández, Reilly, and Kenny 2019). Three groups of multimorbidity patterns – cardiovascular and metabolic diseases, mental health problems, and musculoskeletal disorders – were reported in a systematic review (Prados-Torres et al. 2014) where diabetes was the most prevalent long-term condition, along with chronic obstructive pulmonary disease (COPD) and hypertension. The results indicated that specific long-term conditions played a predominant role in the development of multimorbidity and placed patients at a high risk of polypharmacy in the future.

Polypharmacy has been a crucial issue for older people globally since the identification of its associations with morbidity and mortality in the literature (Hajjar, Cafiero, and Hanlon 2007; Dagli and Sharma 2014). The underlying mechanism has not yet been

confirmed, although the adverse outcomes of polypharmacy may relate to unnecessary medications, adverse drug reactions, drug-drug interactions, drug-disease interactions (treatment conflict), or other unknown factors. As ageing populations are rapidly growing worldwide, the number of older adults with polypharmacy may be greater than has previously been imagined.

The relationship between multimorbidity and polypharmacy has been widely discussed (Wise 2013; Sinnott and Bradley 2015) with the emerging idea of including multimorbidity and polypharmacy in treatment guidelines (National Institute for Health and Care Excellence (NICE) 2017; Muth et al. 2019). NICE not only proposes guidance for multimorbidity management (NICE 2016) but also addresses polypharmacy issues in people with multimorbidity (NICE 2017). The care of older adults is transitioning from a disease-centred approach to patient-centred management.

1.2 Definitions of polypharmacy

At the most basic level, polypharmacy refers to a patient's taking multiple concurrent medications per day. Despite this intuitive understanding of the term, however, more details need to be clarified to provide a clear definition of polypharmacy. The epidemiological concept of the five Ws – who, what, when, where, and why/how – encompasses the aspects that need to be considered in the assessment of medication use:

- Who: patients, who may be children, younger adults, or older adults.
- What: medications being taken, which may include prescribed medications, over-the-counter (OTC) drugs, or medicinal herbs.

- When: the period of the medication, which may range from a few days (short-term) to several months (long-term).
- Where: the locations where medications are prescribed by doctors and/or taken by patients, which may be hospital inpatient or outpatient departments, clinics, nursing homes, or the community.
- Why (or how): the appropriate indication corresponding to the prescribed medication.

To date, no consensus on the definition of polypharmacy has been reached, although there is broad agreement on the approach to the assessment of medication use. A WHO report has suggested defining polypharmacy as taking more than four or five medications for long-term conditions simultaneously (Martial, Mantel-Teeuwisse, and Jansen 2013). This definition focuses on the number of medications rather than on the details of medication use. The NICE guidelines do not provide a specific definition of polypharmacy, but they invoke the concepts of appropriate polypharmacy and problematic polypharmacy (NICE 2017). The former means that prescribed medications are optimised with the best evidence; the latter means that the prescription of multiple drugs is inappropriate, or that the benefit of the prescribed medications is not evident (NICE 2017). Polypharmacy is an inevitable consequence of multimorbidity in older adults, and sometimes is justifiable. A thorough evaluation of polypharmacy is essential to ensure that medications are prescribed based on clinical evidence, and also that the benefits of medications outweigh the harms, conditional on the individual's health status.

In addition to these conceptual definitions, one review article summarised different definitions of polypharmacy dating from 2000 to May 2016 (Masnoon et al. 2017). It divided these definitions into three classifications:

1. Numerical-only definitions (111/138; 80.4%): only the total number of medications was taken into account, and the most common cut-off was five.
2. Numerical definitions that took account of the duration of the therapy or the healthcare setting (15/138; 10.9%): this class of definitions focused on medications in long-term use, ranging from 90 days to 240 days according to the duration of the therapy. Some hospital-based studies defined polypharmacy as a certain number of medications during the hospital stay or at hospital discharge.
3. Descriptive definitions (12/138; 8.7%): this class of definitions was about conceptual rather than cut-off values, and could be classified into several subgroups:
    - ❖ Some definitions involved the co-prescription of multiple medications; therefore, the total number of medications was not specified.
    - ❖ Some definitions relied on the presence of irrational prescription, such as medications without good evidence, potentially inappropriate medications/prescriptions (PIMs/PIPs) (e.g. without indications), medication underuse, and the duplication of medications. For example, appropriate polypharmacy referred to optimised medications for patients with multiple conditions where the medication use agreed with the best evidence.
    - ❖ Other definitions included medications obtained from multiple pharmacies, additional medications prescribed for side effects, and inconsistency between the medications recorded and the medications patients were actually taking (dubbed pseudopolypharmacy).

As discussed above, the majority of definitions of polypharmacy found in the literature are numerical only. This may be attributed to the complexity of defining

polypharmacy beyond a cut-off, which may involve difficulties in study design, information availability, and proper assessment of the rationale for medications. Apart from the emphases on cut-off values and treatment durations identified in the review article (Masnoon et al. 2017), some issues have not been discussed – for instance, OTC medications and combination drugs. OTC medications refer to drugs sold directly to the consumer, without a prescription from a healthcare professional. They may be extractions from herbs, nutritional supplements, or symptom relievers such as painkillers. If OTC drugs were taken into account, the prevalence of polypharmacy would be higher, and this would therefore not be comparable with polypharmacy defined by prescribed medications. OTC medications have usually been excluded in the literature, with some exceptions in certain studies (Huang et al. 2010; Moriarty, Hardy, et al. 2015). Antihistamine, aspirin, calcium, calcium plus vitamin D, and magnesium have reportedly been included in definitions of polypharmacy (Huang et al. 2010; Moriarty, Hardy, et al. 2015) where they might be used for unknown indications. The availability and regulation of OTC drugs differ across countries, resulting in inconsistencies between the definitions used in current studies. This situation also makes the generalisation of the selection criteria for OTC drugs unfeasible. In addition to the sheer regional differences in OTC medications, another difficulty that may arise is that they are not well documented in medical records, and for some people the taking of OTC drugs is probably arbitrary. Incomplete information on OTC medications and their suspected irregular use may therefore lead to bias in polypharmacy research. Although it appears difficult to accommodate OTC medications within definitions of polypharmacy, the concurrent use of OTC medications cannot be ignored completely. In a nationally representative sample of older Irish adults, the use of supplements was found to increase as the prevalence of

polypharmacy increased (Peklar et al. 2017). Moreover, some OTC medications have been proven to interact with prescribed medications: for example, the co-administration of warfarin and aspirin increases the risk of bleeding, and the combination of angiotensin-converting enzyme inhibitors (ACEIs, a kind of antihypertensive) with potassium supplements probably causes life-threatening elevations of potassium in the blood (Barrett, Lucas, and Alexander 2016).

Combination drugs are medications that include two or more active ingredients in a single dosage form. The literature has demonstrated different ways to count combination drugs: either by distinct pharmacological drug (Huang et al. 2010; Strehblow, Smeikal, and Fasching 2014; McAvay et al. 2017) or by pill count (Nobili et al. 2011; Abolhassani et al. 2017). The former counts each distinct pharmacological agent as a medication, regardless of the drug class to which it belongs (Huang et al. 2010; Strehblow, Smeikal, and Fasching 2014; McAvay et al. 2017), while the latter counts fixed-dose combinations as one medication (Nobili et al. 2011; Abolhassani et al. 2017). On the other hand, some studies have counted the number of medications according to drug classes: for instance, three different types of diuretics may be counted as one medication (Yashkin et al. 2018). The features discussed in this section – cut-offs, therapy duration, healthcare settings, OTC medications, and combination drugs – vary across studies and have led to variations in the definition of polypharmacy.

Taking together these key elements in the definition of polypharmacy, this PhD research adopted a rigorous definition that involved the most common/comparable cut-off values of concurrent medications, prescribed medications in long-term use, regularly used OTC drugs, and each active component of a combination drug as a

single medication. More details about the definition of polypharmacy in this PhD research will be elaborated in section 4.2.2.

Specific types of polypharmacy

The term ‘polypharmacy’ is sometimes employed to denote the concurrent use of multiple medications for a particular long-term condition (e.g. antipsychotic polypharmacy) or with a specific pharmacological mechanism (e.g. central nervous system (CNS)-active polypharmacy). A good deal of research has investigated antipsychotic polypharmacy in terms of prevalence rates, prescribing patterns, and the association with health outcomes among youths, adults, or older people (Aly El-Gabry et al. 2018; Gaudiano et al. 2018; Huang et al. 2018; Ijaz et al. 2018; Kadra et al. 2018; Yang et al. 2018; Hou et al. 2019). Most studies have defined antipsychotic polypharmacy as taking two or more antipsychotics (Aly El-Gabry et al. 2018; Huang et al. 2018; Kadra et al. 2018; Yang et al. 2018; Hou et al. 2019), while some have employed a cut-off of four to define complex polypharmacy (Gaudiano et al. 2018). The potential health outcomes associated with antipsychotic polypharmacy remain unclear, although there is emerging research on this topic (Ijaz et al. 2018; Kadra et al. 2018). Furthermore, some studies have investigated the prescribing patterns and prevalence of CNS-active polypharmacy (i.e. psychotropic polypharmacy) – defined as exposure to three or more medications acting on the CNS – in older adults (Morin et al. 2019) or elderly dementia patients (Maust et al. 2021). On the other hand, a few studies have explored other types of polypharmacy, such as polypharmacy with oral antidiabetic agents, classified into one, two, and three or more (Willey et al. 2006), and cardiovascular polypharmacy, defined as taking two or more cardiovascular drugs

(Chao et al. 2015). Combination therapy with different pharmacological medications is common for people with mental illnesses, type 2 diabetes, or cardiovascular diseases (CVDs), which may lead to research on specific types of polypharmacy.

Although the complexity of defining polypharmacy has been recognised, and the relevant issues have been discussed, definitions of polypharmacy remain inconsistent and subject to data availability, study designs, study samples, and research questions.

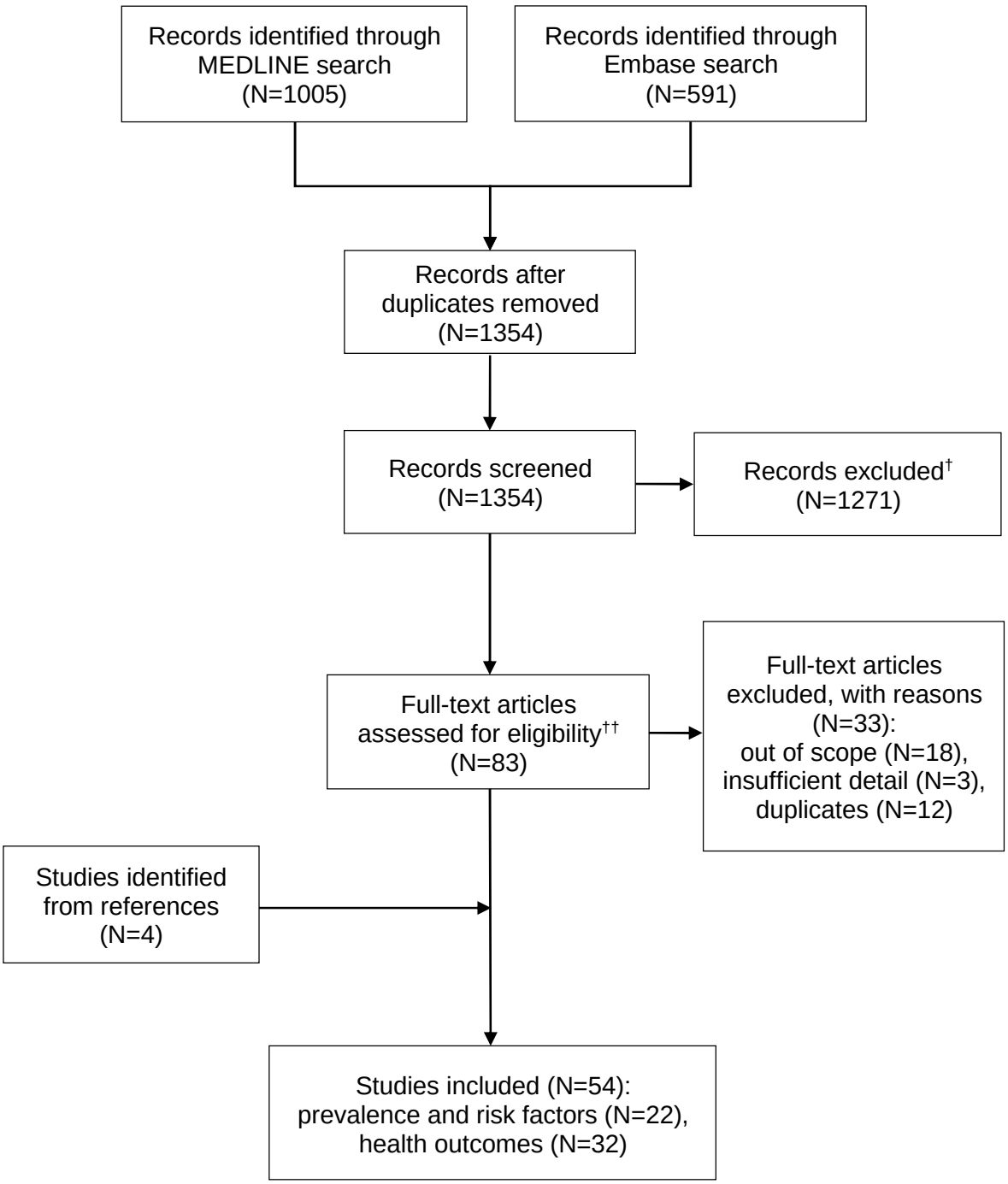
1.3 Polypharmacy research

There is an increase in ageing populations and a concomitant increase in the phenomenon of multimorbidity accompanied by multiple treatments. Therefore, the term ‘polypharmacy’ has been widely used in research to refer to the concurrent daily use of multiple medications. In order to evaluate existing evidence, I carried out a literature search through the MEDLINE and Embase databases, using the search terms ‘polypharmacy’, ‘aged’, ‘prevalence’, ‘risk factors’, and ‘health outcomes’. The relevant subject headings for each search term were also selected in the search process. The literature review reported here covers all aspects of polypharmacy research to provide a broad picture, and it is organised into four sections: prevalence and risk factors, health outcomes, medication-related issues, and intervention. Given the availability of drug information, this PhD research focuses on polypharmacy rather than medication-related issues (e.g. inappropriate prescribing). Thus, polypharmacy research on prevalence, risk factors, and health outcomes in older adults will be discussed in detail. The process of reviewing the polypharmacy literature on

prevalence, risk factors, and health outcomes is shown in Figure 1.1, and that of polypharmacy in general is summarised in Table 1.1.

Polypharmacy has been widely studied among people with specific conditions, from psychiatric, epilepsy, and inflammatory bowel disease patients in the early stages to HIV and cancer patients in recent years. Dementia patients appear to be another interest in polypharmacy studies because of a growing awareness of deprescribing among this vulnerable population; this research has focused on whether fewer medications are prescribed after a dementia diagnosis (Sarkar et al. 2017; Narayan et al. 2019) and on deprescribing interventions (Bravo-Jose, Saez-Lleo, and Peris-Marti 2019; Kase et al. 2019). Further, polypharmacy has also been explored among older adults with particular long-term conditions such as CVDs (Kennel et al. 2019; Tefera, Alemayehu, and Mekonnen 2020), type 2 diabetes (Papazafiropoulou et al. 2014; Noale et al. 2016), chronic kidney disease (Rifkin and Winkelmayer 2010), COPD (Noteboom et al. 2014), and haemophilia (Mannucci et al. 2018). Research has also been reported on a wide range of healthcare settings, from nursing homes (Schneider et al. 2019) and home care (Komiya et al. 2018) to hospital admission (Momo et al. 2019), hospital discharge (Nguyen et al. 2020), and admission through an acute assessment unit (Yong et al. 2012). This literature review focuses on polypharmacy studies among older adults in general, and does not include studies carried out on older adults with particular long-term conditions. The role of diabetes in polypharmacy is reviewed in section 1.4.

Figure 1.1 Flow chart showing the literature review process for polypharmacy in older adults



† Articles that were irrelevant to polypharmacy or not older adult-focused, case reports, and pharmaceutical publications about certain medications were excluded.

†† Criteria were the accessibility of the full text in English and the exploration of risk factors and health outcomes of polypharmacy.

Table 1.1 Summary of previous studies on polypharmacy in older adults

First author	Year, location	Study design	Research outcome	Prevalence/ significance‡	Age	N	Polypharmacy definition		
							Cut-off§	Long-term	Drug criteria
Al-Dahshan A	2020 Qatar	Cross-sectional (population-based‖)	Risk factors	5+: 75.5%	65+	5639	5	−	✓
Badawy NA	2020 Kuwait	Cross-sectional (population-based)	Risk factors	5-8: 58.4% 9+: 10.2%	65+	500	5, 9	−	✓
Ishizaki T	2020 Japan	Cross-sectional (population-based)	Risk factors	5-9: 45.3% 10+: 18.2%	75+	1094199	5, 10	−	−
Suzuki T	2020 Japan	Cross-sectional (population-based)	Risk factors	6: 15.7%	65+	993	6	−	✓
Carmona-Torres JM	2018 Spain	Cross-sectional (population-based‖)	Risk factors	5+: 21.9% 10+: 0.6%	65+	26277	5, 10	−	✓
Slater N	2018 UK	Cross-sectional (population-based‖)	Risk factors	5-9: 24.1% 10+: 6.4%	50+	7730	5, 10	−	✓
Rieckert A	2018 UK, Italy, Austria, Germany	Cross-sectional (population-based)	Risk factors	−	75+	3904	7, 10	✓	−
Sarwar MR	2018 Pakistan	Cross-sectional (population-based)	Risk factors	5-9: 60.8% 10+: 6.2%	65+	385	5, 10	−	−

Table 1.1 (continued)

First author	Year, location	Study design	Research outcome	Prevalence/ significance‡	Age	N	Polypharmacy definition		
							Cut-off§	Long-term	Drug criteria
Vicinanza R	2018 Italy	Cross-sectional (hospital-based)	Risk factors	5+: 39%	50+	476	5	−	−
Pereira KG	2017 Brazil	Cross-sectional (population-based)	Risk factors	5+: 32%	60+	1705	5	−	−
Lim LM	2017 Malaysia	Cross-sectional (population-based‖)	Risk factors	5+: 45.9%	55+	1256	5	−	✓
Castioni J	2017 Switzerland	Cross-sectional (population-based)	Risk factors	5+: 11.8%	40-81	4938	5, 10	✓	✓
Ramos LR	2016 Brazil	Cross-sectional (population-based‖)	Risk factors	5+: 18.0%	60+	6844	5	−	✓
Kojima T	2016 Japan	Cross-sectional (population-based)	Risk factors	6+: 67.1%	− (Mean = 86.6)	1003	6	−	−
Silveira EA	2014 Brazil	Cross-sectional (population-based)	Risk factors	5+: 28%	60+	418	5	−	−

Table 1.1 (continued)

First author	Year, location	Study design	Research outcome	Prevalence/ significance‡	Age	N	Polypharmacy definition		
							Cut-off§	Long-term	Drug criteria
Lu J	2014 China	Cross-sectional (population-based)	Risk factors	2+: 16.5% 5+: 3.7%	90+	859	2, 5	✓	✓
Kim HA	2014 Korea	Cross-sectional (population-based‖)	Risk factors	6+: 86.4% 11+: 44.9% 21+: 3.0%	65+	319185	6, 11, 21	−	−
Santos TR	2013 Brazil	Cross-sectional (population-based)	Risk factors	5+: 26.4%	60+	934	5	−	−
Neves SJ	2013 Brazil	Cross-sectional (population-based)	Risk factors	5+: 11%	60+	400	5	−	✓
Carvalho MFC	2012 Brazil	Cross-sectional (population-based)	Risk factors	5+: 36%	65+	1115	5	−	−
Nomura K	2011 Japan	Cross-sectional (population-based)	Risk factors	5+: 71%	65+	453	5	−	✓
Veehof LJG	2000 Netherlands	Cohort (population-based)	Risk factors	2+: 26.4% → 42% 6+: 1.6% → 4% (start → end)	65+	1544	2, 4, 6	✓	−

Table 1.1 (continued)

First author	Year, location	Study design	Research outcome	Prevalence/ significance‡	Age	N	Polypharmacy definition		
							Cut-off§	Long-term	Drug criteria
Hasan SS	2020 Malaysia	Cross-sectional (population-based)	Frailty	✓	60+	151	5	✓	–
Shmuel S	2019 USA	Cohort (population-based‖)	Incident frailty	✓	50+	1697	5, 10	–	✓
Gutierrez-Valencia M	2018	Systematic review	Frailty	✓	50+†	–	–	–	–
Yuki A	2018 Japan	Cohort (population-based)	Frailty	✓	65+	299	6	–	✓
Katsimpris A	2019	Systematic review	Physical function	✓	50+†	–	–	–	–
Romano-Lieber NS	2019 Brazil	Cohort (population-based‖)	All-cause mortality	✓	60+	1258	5	–	–
Basnet S	2018 USA	Cohort (population-based)	30-day rehospitalisation	✓	65+	25190	C	✓	–
Gutierrez-Valencia M	2017 Spain	Cohort (hospital-based)	Mortality A & E visits Hospitalisations	– ✓ ✓	– (Mean = 88.3)	200	5, 10	–	–

Table 1.1 (continued)

First author	Year, location	Study design	Research outcome	Prevalence/ significance‡	Age	N	Polypharmacy definition		
							Cut-off§	Long-term	Drug criteria
Leelakanok N	2017	Systematic review and meta-analysis	All-cause mortality	✓	–*	–	–	–	–
Hallgren J	2016 Sweden	Cohort (population-based)	Hospitalisation	✓	65+	429	C	–	–
Lu WH	2015 Taiwan	Cohort (population-based)	Mortality All-cause hospitalisations Fracture-specific hospitalisations	– ✓ ✓	65+	59042	5, 10	✓	✓
Sganga F	2015 Italy	Cohort (hospital-based)	Rehospitalisation Mortality	✓ –	65+	480	8	–	–
Best O	2013 Australia	Cross-sectional (hospital-based)	Length of hospital stay Hospitalisations	– –	65+	329	5	✓	✓
Zaninotto P	2020 UK	Cohort (population-based‖)	Fall-related hospitalisations	✓	50+	6220	5, 10	✓	✓

Table 1.1 (continued)

First author	Year, location	Study design	Research outcome	Prevalence/ significance‡	Age	N	Polypharmacy definition		
							Cut-off§	Long-term	Drug criteria
Zia A	2017 Malaysia	Case-control (hospital-based)	Falls	−	65+	202	5	✓	✓
Laflamme L	2015 Sweden	Case-control (population-based‖)	Fall injuries	✓	65+	64399	C, 10+	−	✓
Fonad E	2015 Sweden	Cross-sectional (population-based)	Falls	✓	75+	1193	4	−	−
Chiu MH	2015 Taiwan	Case-control (hospital-based)	Falls	✓	50+	83	6	−	✓
Abreu HC	2015 Brazil	Cohort (hospital-based)	Falls	✓	60+	221	7	−	−
Kojima T	2012 Japan	Cohort (hospital-based)	Falls	✓	65+	172	5	−	−
Kojima T	2011 Japan	Cross-sectional (hospital-based)	Fall risk	✓	65+	262	C	−	−
Lai SW	2010 Taiwan	Case-control (population-based‖)	Hip fracture	✓	65+	2328	5	−	✓

Table 1.1 (continued)

First author	Year, location	Study design	Research outcome	Prevalence/ significance‡	Age	N	Polypharmacy definition		
							Cut-off§	Long-term	Drug criteria
Baranzini F	2009 Italy	Cross-sectional (population-based)	Fall-related injuries	✓#	65+	293	7	−	✓
Ziere G	2006 Netherlands	Cross-sectional (population-based)	Falls	✓#	55+	6928	4	−	−
Leszek S	2016 Poland	Cross-sectional (hospital-based)	Depressive symptoms	✓	65+	206	C	−	−
Park HY	2017 South Korea	Case-control (population-based‖)	Dementia	✓	65+	5562	5	−	−
Lai SW	2012 Taiwan	Case-control (population-based‖)	Dementia	✓	65+	7135	5	−	✓
Niikawa H	2017 Japan	Cross-sectional (population-based)	Cognitive impairment	✓	65+	1152	6	−	✓
Ahmed B	2014 Pakistan	Cohort (hospital-based)	Adverse drug reactions	✓	65+	1000	5	−	✓
Kojima T	2012 Japan	Cross-sectional (hospital-based)	Adverse drug reactions	✓	65+	2412	6	−	−

Table 1.1 (continued)

First author	Year, location	Study design	Research outcome	Prevalence/ significance[‡]	Age	N	Polypharmacy definition		
							Cut-off[§]	Long-term	Drug criteria
Wang R	2015 China	Cohort (hospital-based)	Mortality	✓	80+	1562	6, 10	✓	✓
			Adverse drug reactions	✓					
			Falls	✓					
			Frailty	✓					
			Disability	✓					
			Cognitive impairment	−					
Fried TR	2014	Systematic review	Hospitalisation Mortality Adverse drug events Falls Measures of function and cognition	Mixed	−[**]	−	−	−	−

Table 1.1 (footnotes)

‡ Symbol '✓' referred to having significant results; symbol '−' referred to having non-significant results.

‖ Representative sample employed.

§ C uses total number of medications rather than polypharmacy cut-offs.

† Youngest cut-off was 50, but most studies were 65+.

* Including people aged 16+ (a few studies) or specific populations such as HIV-infected and seizure patients.

** A few studies included people aged 18+; most studies based on community-dwelling older adults.

Fall risk was associated with polypharmacy use, but only when at least one established fall risk-increasing drug was part of the daily regimen.

1.3.1 Prevalence and risk factors

The phenomenon of polypharmacy has been increasing for decades among not only older people but also younger adults (van den Akker et al. 2019). The reported prevalence of polypharmacy (five or more medications) ranges from 11% to 75.5% among older adults (Nomura et al. 2011; Carvalho et al. 2012; Neves et al. 2013; Santos et al. 2013; Silveira, Dalastra, and Pagotto 2014; Ramos et al. 2016; Castioni et al. 2017; Lim et al. 2017; Pereira et al. 2017; Carmona-Torres et al. 2018; Sarwar, Iftikhar, and Sarfraz 2018; Vicinanza et al. 2018; Wastesson et al. 2018; Al-Dahshan et al. 2020; Badawy et al. 2020; Ishizaki et al. 2020); the reported prevalence of excessive polypharmacy (10 or more medications) varies between 0.6% and 18.2% (Carmona-Torres et al. 2018; Sarwar, Iftikhar, and Sarfraz 2018; Wastesson et al. 2018; Ishizaki et al. 2020). Two studies have reported a much lower prevalence of polypharmacy than others: 4% for six or more medications in a Dutch study, where only medications in long-term use (more than 240 days a year) were included (Veehof et al. 2000); 3.7% for five or more medications among adults aged 90 and older living in rural China (Lu et al. 2014). A few studies have been based on older adults with diabetes, where the prevalence of polypharmacy was found to be 57.1% (with a cut-off of five) (Noale et al. 2016), 66% (cut-off of five) (Ribeiro Da Silva et al. 2016), 79% (cut-off of six) (Papazafiropoulou et al. 2014), and 84% (cut-off of four) (Gadsby et al. 2012). These findings indicate that older diabetes patients tend to have polypharmacy. The huge variation in the prevalence of polypharmacy in the literature may be shaped by different study designs (e.g. age ranges), locations (e.g. healthcare systems), study populations (e.g. representative samples), or even non-numerical definitions of polypharmacy, such as therapy duration and inclusion criteria for medications. Although a few studies have used representative samples, the variation in the

prevalence of polypharmacy (five or more) is still noticeable, ranging from 18.0% to 75.5% (Ramos et al. 2016; Lim et al. 2017; Carmona-Torres et al. 2018; Slater et al. 2018; Al-Dahshan et al. 2020). Only two of these studies reported the prevalence of heightened polypharmacy (10 or more): 6.4% in the UK (Slater et al. 2018) and 0.6% in Spain (Carmona-Torres et al. 2018). Further, a nationally representative Korean study (Kim et al. 2014) reported that among the population, 86.4% took six medications or more, 44.9% took 11 or more, and 3.0% took 21 or more; these figures were much higher than those found in other studies. There is thus little agreement on the prevalence of polypharmacy, even among studies with representative samples.

A wide range of factors associated with polypharmacy (including higher levels of polypharmacy) has been reported, from socio-demographics to health-related factors and health service utilisation. Older age is generally thought to contribute to polypharmacy (Veehof et al. 2000; Carvalho et al. 2012; Santos et al. 2013; Ramos et al. 2016; Castioni et al. 2017; Lim et al. 2017; Pereira et al. 2017; Carmona-Torres et al. 2018; Slater et al. 2018; Vicinanza et al. 2018; Ishizaki et al. 2020), although people aged 80 years, 85 years, or more have been reported to have a lower risk of polypharmacy (Kim et al. 2014; Silveira, Dalastra, and Pagotto 2014; Rieckert et al. 2018). Females have been shown to be likely to develop polypharmacy in most studies (Nomura et al. 2011; Carvalho et al. 2012; Santos et al. 2013; Silveira, Dalastra, and Pagotto 2014; Pereira et al. 2017; Carmona-Torres et al. 2018; Al-Dahshan et al. 2020; Badawy et al. 2020), whereas males have been found to have a higher risk in a few studies (Kim et al. 2014; Lim et al. 2017; Ishizaki et al. 2020). Several studies have found an association between polypharmacy and a lower level or lack of education among older adults (Neves et al. 2013; Lu et al. 2014; Castioni et al. 2017; Carmona-Torres et al. 2018; Sarwar, Iftikhar, and Sarfraz 2018; Badawy et al. 2020). Rare

studies have reported on other characteristics, such as ethnicity (Lim et al. 2017), working status (Carvalho et al. 2012), marital status (separated/divorced/widowed) (Santos et al. 2013; Carmona-Torres et al. 2018), and income/wealth (with mixed findings) (Carvalho et al. 2012; Kim et al. 2014; Slater et al. 2018). However, gender and education were not related to polypharmacy in a study exploring the risk factors for excessive polypharmacy among older people with polypharmacy (Rieckert et al. 2018). This study only included people with polypharmacy, and thus differed from the comparisons between polypharmacy and non-polypharmacy made in other studies.

In addition, polypharmacy's health-related characteristics have been extensively identified. The literature suggests that a greater number of comorbidities plays a key role in the development of polypharmacy (Nomura et al. 2011; Neves et al. 2013; Kim et al. 2014; Silveira, Dalastra, and Pagotto 2014; Kojima et al. 2016; Lim et al. 2017; Rieckert et al. 2018; Al-Dahshan et al. 2020; Badawy et al. 2020). Particular long-term conditions have been found to make a significant contribution to polypharmacy, such as CVDs, diabetes, and dyslipidaemia (Veehof et al. 2000; Carvalho et al. 2012; Kim et al. 2014; Lu et al. 2014; Ramos et al. 2016; Lim et al. 2017; Vicinanza et al. 2018; Al-Dahshan et al. 2020). A higher body mass index (BMI) (with a cut-off of 30 in some research) has been shown to be an important risk factor for polypharmacy (Silveira, Dalastra, and Pagotto 2014; Castioni et al. 2017; Carmona-Torres et al. 2018; Rieckert et al. 2018; Slater et al. 2018; Al-Dahshan et al. 2020), along with poor self-rated health (Carvalho et al. 2012; Neves et al. 2013; Santos et al. 2013; Silveira, Dalastra, and Pagotto 2014; Ramos et al. 2016; Pereira et al. 2017; Slater et al. 2018). By contrast, there seems to be a lack of agreement regarding other health factors that have been reported in only a few studies, including frailty (Rieckert et al. 2018), cognitive impairment (Lu et al. 2014), poor physical and mental health (Rieckert et al. 2018),

smoking (being a former or current smoker) (Castioni et al. 2017), alcohol consumption (showing an inverse effect) (Slater et al. 2018), medium to low adherence to the Mediterranean diet (Vicinanza et al. 2018), eutrophic nutritional status (Silveira, Dalastra, and Pagotto 2014), and bedridden status (Carmona-Torres et al. 2018). Some drug-related factors have also been reported to be related to polypharmacy: the number of medications at the baseline (Veehof et al. 2000), medications without a clear indication (Veehof et al. 2000), self-medication (Carmona-Torres et al. 2018), and the use of analgesics, diuretics, or antidiabetics (Ishizaki et al. 2020). Furthermore, health service utilisation behaviours have been found to contribute to polypharmacy in some ways. Older people who consult more medical institutions (Kojima et al. 2016; Badawy et al. 2020; Ishizaki et al. 2020; Suzuki et al. 2020), have more medical appointments (Neves et al. 2013; Richardson, Kenny, and Bennett 2014; Pereira et al. 2017), are admitted to hospital more frequently (Ramos et al. 2016; Badawy et al. 2020; Ishizaki et al. 2020), use physician home visits (Ishizaki et al. 2020), or have free healthcare (an Irish study) (Richardson, Kenny, and Bennett 2014) are reportedly more likely to show polypharmacy. Conversely, older adults who utilise only the public health system (Carvalho et al. 2012) and residents with higher care need levels in long-term care facilities (Kojima et al. 2016) are reportedly less likely to show polypharmacy. Lastly, physician factors have been related to less polypharmacy and inappropriate prescribing, in terms of their considering the number of medications and the relevant benefits or risks, and their utilisation of the Beers criteria (Ie et al. 2017).

The risk factors identified in different studies vary and may depend on the study designs and populations (including sample sizes), healthcare systems, definitions of polypharmacy, and data availability. The inconsistent adjustment to potential

confounders across the studies may have contributed to the lack of agreement on factors associated with polypharmacy, except for the higher number of comorbidities. Also, social determinants were less likely to be considered comprehensively in the literature, probably because of data availability or study design. Thus, more studies with a representative sample of older adults and comprehensive information on socio-demographics and health determinants are warranted to understand which characteristics of older people are related to a high risk of polypharmacy.

1.3.2 Health outcomes

A broad spectrum of health outcomes has been studied in relation to polypharmacy among older adults, from physical health (e.g. frailty) to psychological well-being (e.g. depression). Although these studies have investigated the potential consequences of polypharmacy, differences in study design (e.g. age ranges), definitions of polypharmacy, and measurements of health lead to difficulties in making direct comparisons among studies. Relevant studies of associations between polypharmacy and health outcomes in older adults are summarised in Table 1.1. Most of the literature suggests that older adults with polypharmacy are prone to be frail, be hospitalised frequently, die early, or report falls, as polypharmacy itself is regarded as a geriatric symptom. In addition to these main outcomes, polypharmacy has been found to be related to dementia (Lai et al. 2012; Park et al. 2017), cognitive impairment (Niikawa et al. 2017), significant depressive symptoms (Leszek, Jadwiga, and Agnieszka 2016), disability (Wang et al. 2015), and adverse drug reactions (Kojima, Akishita, Kameyama, et al. 2012; Ahmed et al. 2014; Wang et al. 2015). Some studies based on older adults with polypharmacy have shown that taking more medications is associated with poorer health-related quality of life in this population (Montiel-Luque

et al. 2017; Tegegn et al. 2019). On the other hand, the influence of polypharmacy on older people's nutritional status is also a concern but remains unclear according to the present evidence (Jyrkka et al. 2012; Zadak et al. 2013). In the following paragraphs, the main outcomes of polypharmacy – frailty and physical function, falls, and hospitalisation and mortality – will be discussed.

Frailty and physical function

A systematic review on frailty (Gutierrez-Valencia et al. 2018) has suggested that polypharmacy may contribute to the development of frailty, although the causality is uncertain and may be bidirectional. Among the studies included in this review, around one third were longitudinal studies, and the rest were cross-sectional. A positive correlation between polypharmacy and frailty was also found in three cohort studies (Wang et al. 2015; Yuki et al. 2018; Shmuel et al. 2019) and one cross-sectional study (Hasan et al. 2020). Moreover, one systematic review (Katsimpris et al. 2019) indicated a strong bidirectional relationship between polypharmacy and physical function in older people. This review only included observational studies, and some limitations should be acknowledged. Variations in the definitions of polypharmacy and the measurements of physical function made direct comparisons challenging, and the constant status of polypharmacy and physical function rather than time-varying conditions may have led to research biases.

Falls

The relationship between polypharmacy and falls has been widely identified in the literature (Kojima, Akishita, Nakamura, et al. 2012; Abreu et al. 2015; Chiu et al. 2015;

Fonad, Robins Wahlin, and Rydholm Hedman 2015; Laflamme et al. 2015; Wang et al. 2015), although a Malaysian study found that the use of two or more fall risk-increasing drugs (e.g. antidepressants) was a risk factor for falls instead of polypharmacy (Zia, Kamaruzzaman, and Tan 2017). Three other studies (Ziere et al. 2006; Baranzini et al. 2009; Richardson, Bennett, and Kenny 2014) somewhat agreed with the findings regarding fall risk-increasing drugs and reported that falls were related to polypharmacy only when at least one fall risk-increasing drug was part of the daily regimen. Further, the fall risk index (Kojima et al. 2011), hip fractures (Lai et al. 2010), fracture-specific hospital admissions (Lu et al. 2015), and fall-related hospital admissions (Zaninotto et al. 2020) were also found to be significantly related to polypharmacy. I was involved in Zaninotto et al.'s study, to which I contributed by analysing the data on medications and refining the definitions of polypharmacy and heightened polypharmacy – the same definitions were also adopted in this PhD work. The risk of hospitalisation due to a fall increased with polypharmacy status, even when underlying health conditions and fall risk-increasing drugs were taken into account.

Hospitalisation and mortality

Older adults with polypharmacy have been found to have a high risk of hospitalisation (Lu et al. 2015; Hallgren et al. 2016; Gutierrez-Valencia et al. 2017), rehospitalisation (Sganga et al. 2015; Basnet et al. 2018), and visits to accident and emergency (A & E) departments (Gutierrez-Valencia et al. 2017), but the association between polypharmacy and mortality is less consistent. Some studies have shown no relationship between polypharmacy and all-cause mortality (Lu et al. 2015; Sganga et al. 2015; Gutierrez-Valencia et al. 2017), whereas others have shown a positive

correlation (Wang et al. 2015; Romano-Lieber et al. 2019). One meta-analysis (Leelakanok et al. 2017) suggested that polypharmacy was associated with an increased risk of all-cause mortality, but this analysis involved a wide range of populations such as young adults aged 16 and over, HIV-infected people, and seizure patients, which may hamper the generalisation of the results to community-dwelling older adults. Meanwhile, a cross-sectional study (Best et al. 2013) failed to find an association between polypharmacy and hospital admission or length of hospital stay; however, the study design makes the results less persuasive. The current evidence suggests that the effect of polypharmacy on all-cause mortality in older adults remains controversial. There has been no relevant research on cause-specific mortality.

A systematic review investigating a range of outcomes in community-dwelling older adults (Fried et al. 2014) provided mixed evidence on the associations between polypharmacy and falls, adverse drug events, hospitalisation, mortality, and measures of function and cognition. Different adjustments to comorbidities across studies would influence the quality of the analyses, probably resulting in mixed findings. On the other hand, intensive drug therapy (equivalent to polypharmacy) – defined as the concurrent use of five or more distinct drug categories of antidiabetic or antihypertensive medications – appears to be beneficial for older people with diabetes and hypertension (Yashkin et al. 2018). Intensive drug therapy was associated with a lower risk of all-cause mortality but a higher risk of macrovascular outcomes such as congestive heart failure and myocardial infarction. This study also suggested that adherence to the screening recommendations of the American Diabetes Association (ADA) could significantly reduce mortality and macrovascular events in older diabetes patients (Yashkin et al. 2018). Thus, intensive drug therapy was regarded as protective, and

its benefits were likely to outweigh the harms to which polypharmacy might give rise among high-risk older adults.

Apart from the direct link between polypharmacy and potential consequences, some medications have been reported to impose negative impacts on older people on medication. Anticholinergic drugs have been found to increase the risk of short-term (six-month) cognitive decline (Wu et al. 2017), injurious falls (Richardson et al. 2015), and mortality (Sarbacker et al. 2017). Older adults who take psychotropic drugs (primarily antidepressants and benzodiazepines (BZDs)), diuretics, and opioids are prone to experience falls (Chiu et al. 2015; Du, Wolf, and Knopf 2017; Marron et al. 2019; Donoghue et al. 2020). Psychotropics have also been linked to orthostatic hypotension (Press, Punchik, and Freud 2016), cerebrovascular events (Franchi et al. 2013), and all-cause hospitalisations (Makris et al. 2015). Moreover, other medications are reported to be associated with adverse outcomes: α blockers and calcium channel blockers (CCBs) with orthostatic hypotension (Press, Punchik, and Freud 2016), opioids with all-cause hospitalisations, skeletal muscle relaxants with A & E visits and all-cause mortality, and antihistamines with A & E visits (Makris et al. 2015). The evidence regarding the relationships among polypharmacy, specific medications, and health outcomes is scarce and currently lacks agreement. As there is a rising trend in the concomitant use of analgesics and psychotropics among home-dwelling older people (Hartikainen et al. 2005), the effect of particular medications on older adults' health needs more research and evidence.

In summary, polypharmacy in older adults appears to have negative health effects in different ways but may benefit people with particular long-term conditions (e.g. diabetes and hypertension). The mixed findings from the literature imply that polypharmacy's effects on older people are controversial and uncertain. Also, the role

of diabetes in the association between polypharmacy and health outcomes remains unclear. In addition to polypharmacy status, specific medications may pose a risk of adverse outcomes for older people, but very little is known so far. As a result, more evidence is warranted to better understand how polypharmacy influences older adults' health and the role of diabetes and specific medications.

1.3.3 Medication-related issues

Medication-related problems have drawn public attention as polypharmacy has become prevalent among older adults. A higher number of concurrent medications is likely to prompt medication-related problems that may undermine the benefits of the medications. Four main issues are discussed below.

PIMs/PIPs

Among the medication-related problems that may arise from polypharmacy, PIMs/PIPs are the most commonly researched topics. PIMs studies have been done on older adults who live in care homes or nursing homes (Chen et al. 2012; Nascimento et al. 2014; Storms et al. 2017; Chun, Appel, and Simmons 2018; Ivanova et al. 2018), are admitted to hospital (Liu et al. 2012; McMahon et al. 2014; Formiga et al. 2016; Marques et al. 2018; Alhawassi, Alatawi, and Alwhaibi 2019; Bo et al. 2019), or are recorded in community or primary care database (Galvin et al. 2014; Moriarty, Hardy, et al. 2015; Heider et al. 2018; Masumoto et al. 2018; Huang et al. 2019; Hucteau et al. 2019; Martinez, Abner, and Moga 2019; Achterhof et al. 2020; de Araujo et al. 2020; Lopez-Rodriguez et al. 2020). Three common tools for defining PIMs are the Beers criteria of the American Geriatrics Society (versions 2015, 2019)

(By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel 2019), the Screening Tool of Older People's Prescriptions (known as STOPP) and Screening Tool to Alert to Right Treatment (known as START) criteria (versions 2008, 2014) (O'Mahony et al. 2015), and the Medication Appropriateness Index criteria (Samsa et al. 1994). PIMs have shown an increasing trend over recent years (Moriarty, Bennett, et al. 2015; Moriarty, Hardy, et al. 2015) with a prevalence varying from 14.6% to 93.2% across studies (Chen et al. 2012; Liu et al. 2012; Galvin et al. 2014; McMahon et al. 2014; Nascimento et al. 2014; Moriarty, Hardy, et al. 2015; Formiga et al. 2016; Storms et al. 2017; Chun, Appel, and Simmons 2018; Ivanova et al. 2018; Marques et al. 2018; Masumoto et al. 2018; Alhawassi, Alatawi, and Alwhaibi 2019; Bo et al. 2019; Huang et al. 2019; Hucteau et al. 2019; Martinez, Abner, and Moga 2019; Achterhof et al. 2020; Lopez-Rodriguez et al. 2020). Different study samples, study designs (e.g. age ranges), and assessment tools may have contributed to the variation in the prevalence. Polypharmacy has been found to be associated with PIMs, along with several long-term conditions such as diabetes, heart failure, and anxiety (Formiga et al. 2016; Alhawassi, Alatawi, and Alwhaibi 2019; de Araujo et al. 2020). A link between PIMs and adverse outcomes is still uncertain, although many health outcomes have been studied. PIMs have been found not to be related to falls, mortality, or hospitalisations (Chun, Appel, and Simmons 2018; Ivanova et al. 2018; de Araujo et al. 2020), but to be associated with falls in older people with polypharmacy (Masumoto et al. 2018). It has been found that older adults with PIMs are likely to become dependent (Hucteau et al. 2019) and to have more A & E and general practitioner (GP) visits (Moriarty et al. 2016), but no relationship has been found with cognitive or functional decline (Martinez, Abner, and Moga 2019). Further, the association between PIMs and adverse health outcomes (e.g. A & E and GP visits) has been found to be

exclusively present among older adults (65 years and older) (Moriarty et al. 2016) but not middle-aged people (aged 45–64 years) (Moriarty et al. 2017), although PIMs are prevalent in both populations. More importantly, the relationship between PIMs and health consequences can differ substantially when different PIMs assessment tools are used, such as mortality and hospitalisations (Huang et al. 2019), A & E and GP visits, quality of life, and functional decline (Moriarty et al. 2020). Apart from the health outcomes, the use of PIMs has been found to increase healthcare costs (Cahir et al. 2010; Heider et al. 2018), and therefore relevant interventions have also been explored. Several interventions in PIMs – the interdisciplinary co-managed care concept (Gleich et al. 2019), computerised decision support tools (Monteiro et al. 2019), and an electronic clinical decision support system (Rogero-Blanco et al. 2020) – have been found to be helpful in detecting PIMs and subsequently reducing their prescription.

Drug-drug interactions

Drug-drug interactions are an important issue for older people with polypharmacy and seem to be unavoidable. Drug-drug interactions can be classified into three categories according to severity: major, moderate, and minor (Aronson 2007). The research therefore emphasises clinically relevant drug-drug interactions. The literature has established the relationship between polypharmacy and drug-drug interactions in older people (Castilho et al. 2018; Yoon et al. 2018; Dias, Santos, and Reis 2019; Hamada et al. 2019; Iniesta-Navalon et al. 2019). Non-steroidal anti-inflammatory drugs (NSAIDs) appear to be the most frequent driver of clinically relevant drug-drug interactions, either in combination with corticosteroids or with angiotensin II receptor

blockers (ARBs)/ACEIs (Yoon et al. 2018; Iniesta-Navalon et al. 2019; Souty et al. 2020). The importance of drug safety among older adults has been recognised; therefore, it is advisable to examine drug-drug interactions in a medication review and geriatric assessment (Tomita et al. 2019). Some campaigns have also been developed to contain the burden of drug-drug interactions for older people with polypharmacy (Raschi et al. 2015). On the other hand, drug-nutrient interactions are an emerging concern, since a synergistic negative effect of polypharmacy and malnutrition on older adults has been confirmed (Little 2018), but little information on drug-nutrient interactions is currently available.

Adverse drug reactions/medication-related problems

Adverse drug reactions, also known as side effects, are defined as noxious and unintended responses to a drug at normally used doses for therapeutic purposes. The terms ‘medication-related problem’ and ‘medication-related harm’ are also commonly used to refer not only to adverse drug reactions but also to harms arising from medication error or from a failure to receive medication owing to non-adherence (Parekh et al. 2018). Relevant research has often been conducted at hospital admission (Ognibene et al. 2018; Kojima et al. 2020) or discharge (Parekh et al. 2018); in these instances, the prevalence of adverse drug reactions has varied from 6.1% to 37%, with a higher incidence among outpatients than inpatients (Undela, Joshi, and Ramesh 2017). Adverse drug reactions seem to be individualised and hard to generalise, since different medications have been reported to cause adverse reactions. Diuretics, antithrombotics, and CNS-active drugs were found to be the most common drivers of adverse drug reactions in an Italian study (Ognibene et al. 2018),

while opiates, antibiotics, and BZDs were found to be high-risk in a UK study (Parekh et al. 2018). Overall, polypharmacy is related to adverse drug reactions that prompt hospital admission and consequently lead to severe adverse outcomes (e.g. death and disability) and substantial use of healthcare resources (Ognibene et al. 2018; Parekh et al. 2018; Kojima et al. 2020).

Medication adherence

Polypharmacy has been found to negatively influence medication adherence among older adults (Gellad, Grenard, and Marcum 2011; Vatcharavongvan and Puttawanchai 2017; Vicente-Sanchez et al. 2018). A Thai study found a high prevalence of poor medication adherence (61%) in older people with polypharmacy (Vatcharavongvan and Puttawanchai 2017). Other potential barriers to adherence were also reported in a systematic review, including patient-related factors (e.g. knowledge of diseases, health literacy, and cognitive function), drug-related factors (e.g. adverse effects), the patient-provider relationship, and various logistical barriers to obtaining medications, but no systematic conclusion regarding potential barriers could be drawn (Gellad, Grenard, and Marcum 2011). Diabetes and its treatment seem to be a prognostic factor for poor adherence (Vicente-Sanchez et al. 2018), and therefore many studies have exclusively targeted type 2 diabetes patients. Furthermore, the use of non-prescription (i.e. OTC) medications has been found to contribute to non-adherence to prescribed medications (Anoopkumar-Dukie et al. 2020). To ensure optimal outcomes for older adults with polypharmacy, interventions in medication adherence have been explored. The theoretical domains framework of behaviour has been used to systematically identify the determinants of medication adherence, thereby helping to

develop potential interventions (Patton et al. 2018). Effective education on medication adherence has also been confirmed to improve health literacy and consequently improve medication adherence among adults (Tan, Cheng, and Siah 2019).

1.3.4 Interventions

A variety of interventions in polypharmacy for older people have been conducted to date, although an agreed and validated polypharmacy tool is still lacking. Thus, approaches to the definition and assessment of polypharmacy may vary in practice. Increasing evidence has suggested that beyond the number of medications, medication- and patient-related factors are equally important for the assessment of polypharmacy (Masnoon et al. 2019; Masnoon et al. 2020). A systematic review has pointed out that specific drug classes, such as sedatives, anticholinergics, opioids, and systemic corticosteroids, need to be involved in polypharmacy assessments (Masnoon et al. 2019). Given the lack of validated tools of polypharmacy, strategies that incorporate medication- and patient-related factors are warranted to facilitate the rationalisation of polypharmacy (Masnoon et al. 2020).

Medication reviews are regarded as the standard approach to the management of medication optimisation, including polypharmacy issues among older adults, and they are advocated by NICE (NICE 2020), National Health Service (NHS) Scotland (NHS Scotland 2020), and NHS England (NHS England and NHS Improvement 2019). However, the effectiveness of medication reviews seems to be unclear according to the current literature. A meta-analysis of randomised clinical trials showed that medication reviews that included a comprehensive clinical evaluation for disease management reduced hospitalisations in older adults with polypharmacy (Mizokami et al. 2019). By contrast, other systematic reviews have suggested that medication

reviews may be useful for the identification and reduction of medication-related problems but that their effect on clinical outcomes remains uncertain (Johansson et al. 2016; Beuscart et al. 2017; Chen et al. 2019). Different patient-perceived barriers to medication reviews have been reported, including a lack of resources for GP-led interventions and a lack of confidence in pharmacists' expertise for pharmacist-led interventions, although patients think that medication reviews are helpful for double-checking the indications for medicines and potential drug-drug interactions (Uhl et al. 2018). Community-dwelling older people have expressed an interest in being involved in their medication assessments (Holmqvist et al. 2019), but their awareness of their active role in addressing polypharmacy needs to be improved, indicating the necessity to improve older adults' communication skills (Schopf et al. 2018). Furthermore, to popularise and facilitate medication reviews in practice, NHS Scotland has launched a digital app that provides up-to-date and evidence-based guidance for users (Barnett et al. 2020). Although the app has been found to identify 23% fewer drug-related problems than the usual pharmacist care, the benefits of its high accessibility (in all care settings) are acknowledged (Barnett et al. 2020).

Pharmacist services

Pharmacists have been involved in many interventions in polypharmacy for older adults, and most of these interventions have shown promising results. Pharmacist-led interventions have been found to contribute to medication appropriateness and consequently to decrease polypharmacy, drug-related problems, PIPs, and fall rates, regardless of healthcare setting (e.g. nursing home or hospital) (Gutierrez-Valencia et al. 2019; Lee, Mak, and Tang 2019; Hashimoto et al. 2020). Medication counts and

concerning drug-drug interactions (i.e. interactions that should be avoided) have been reduced through a collaborative care approach between GPs and clinical pharmacists (Stuhec, Gorenc, and Zelko 2019). Both pharmacist-led and pharmacist-physician medication optimisation interventions for older people with polypharmacy have shown cost savings in randomised controlled trials, indicating that they are cost-effective alternatives to standard care (Lin et al. 2018; Campins et al. 2019). In addition to physicians and pharmacists, the involvement of nurses has been reported to be helpful for identifying, intervening in, and improving medication use (Diggins 2019; Lagerin et al. 2020).

Deprescribing

Deprescribing seems to be a key element in polypharmacy interventions and has been discussed extensively for older people with limited life expectancy (Lundby et al. 2019; Paque et al. 2019). A rule of thumb for deprescribing is that the harm of the medication outweighs the benefits (Potter et al. 2019). GPs have therefore been found to be willing to deprescribe cardiovascular preventive medications in the absence of corresponding indications, but they tend to retain drugs for pain management among people aged 80 and older (Mantelli et al. 2018). Patient involvement and coordination of care have also been identified as key factors in deprescribing (Zechmann et al. 2019). Older adults who are concerned about their number of drugs, who experience adverse effects, who believe that one or more of the medications are redundant, or who take 10 or more medications have shown positive attitudes towards deprescribing (Gillespie, Mullan, and Harrison 2019). Furthermore, adequate training in deprescribing is necessary for medical staff. Educational interventions in outpatient

medication management and a framework for deprescribing have been delivered to internal medicine residents and nurse practitioners and have proved to improve medical workers' knowledge, skills, and attitudes towards deprescribing (Brett and Graham 2018; Mecca et al. 2019). Several approaches to the rationalisation of medication in hospital contexts have been found to be feasible and effective, such as a deprescribing checklist (Pourhadi, Pearson, and Tacey 2020) and a pharmacist-led, physician-supported deprescribing model (Potter et al. 2019). Although the concept of deprescribing is widespread, its impact on clinical outcomes in older adults with polypharmacy may need more evidence.

1.4 The role of diabetes in polypharmacy

As mentioned in section 1.1.2, diabetes is one of the long-term conditions that tend to develop multimorbidity (Prados-Torres et al. 2014). Diabetes was also found to be prone to coexist with other conditions in a systematic review (Xu, Mishra, and Jones 2017). It has been found that people with diabetes are more likely to develop multimorbidity that includes both physical and mental illnesses than people without diabetes (Zghebi et al. 2020), and to develop future functional impairment (Donoghue, Leahy, and Kenny 2021). Diabetes therefore plays an important role in the development of multimorbidity, and it further results in polypharmacy. This section will focus on the issue of diabetes in older adults, from diabetes and diabetes management to polypharmacy and diabetes.

1.4.1 Diabetes in older adults

The average prevalence of diabetes worldwide in adults aged over 18 years rose from 4.7% (108 million) in 1980 to 8.5% (422 million) in 2014 (WHO 2016). The UK has shown a similar trend, with the prevalence rising from 2.4% in 1994 to 6.2% in 2014 and 6.5% in 2017 among adults aged 16 and older. Among this population, older adults reported a higher prevalence of doctor-diagnosed diabetes than younger adults: 8% of those aged 45–64 years and 15% of those aged 65 and over reported doctor-diagnosed diabetes in 2017 (NHS Digital 2018). Apart from diagnosed diabetes, undiagnosed diabetes, which primarily refers to type 2 diabetes, is also a concern. The prevalence of undiagnosed diabetes among adults (aged 20–79) varies across different regions globally, with the highest figure at 20.5% (Beagley et al. 2014). However, undiagnosed diabetes among older people is not well understood. Using different definitions of undiagnosed diabetes, the limited evidence shows that its prevalence in older adults varies from 0.9% to 13.2% (Harris and Eastman 2000; Dankner et al. 2009; Pierce et al. 2009; Leahy et al. 2015; Sinnott et al. 2015). Two nationally representative studies, the Irish Longitudinal Study on Ageing (TILDA) (Leahy et al. 2015) and the English Longitudinal Study of Ageing (ELSA) (Pierce et al. 2009), reported the prevalence of undiagnosed diabetes as 0.9% and 1.7% respectively. TILDA employed glycated haemoglobin (HbA1c) of 48 mmol/mol (6.5%) and higher as a diagnostic criterion for undiagnosed diabetes, while ELSA used eight-hour fasting glucose of 7.0 mmol/L or higher. These statistics indicate that diabetes seems to be more prevalent among older adults, but the information about undiagnosed diabetes in this vulnerable group is insufficient.

Exposure to undiagnosed diabetes – that is, where the diabetes is unknown and untreated – is likely to accelerate the progression of diabetic complications, which are

defined as injurious effects of hyperglycaemia. The evidence suggests that diabetic complications may progress during the early, undiagnosed phase of diabetes, because such complications are common in people with newly diagnosed diabetes (Harris and Eastman 2000; WHO 2016; Diabetes Canada Clinical Practice Guidelines Expert Committee et al. 2018). Diabetic complications are a major source of mortality and morbidity for diabetes patients and can be divided into two categories (Fowler 2008). Microvascular complications include diabetic retinopathy, nephropathy, and neuropathy; macrovascular complications refer to coronary artery disease, peripheral arterial disease, and stroke (Fowler 2008). As a result, people with undiagnosed diabetes are at high risk of developing diabetic complications and may develop multimorbidity and polypharmacy in the future.

More importantly, the direct effects of ageing on metabolic regulation aggravate the underlying pathophysiology of type 2 diabetes in ageing populations (LeRoith et al. 2019). The occurrence of type 2 diabetes in older adults is a result of complex interactions among genetic, lifestyle, and ageing effects (Lee and Halter 2017) that influence β-cell insulin secretory capacity and tissue sensitivity to insulin (Chang and Halter 2003; Lee and Halter 2017). Ageing effects also interact with diabetes to accelerate the progression of diabetic complications (LeRoith et al. 2019), as comorbidities and ageing-related functional impairments complicate the occurrence of diabetes in older people (Lee and Halter 2017). Thus, diabetes in older adults shows considerable heterogeneity in its pathophysiology, clinical features, and rate of progression (LeRoith et al. 2019).

1.4.2 Diabetes management in older adults

The two world-leading guidelines on the management of diabetes – ADA and NICE (NICE 2015; ADA 2018) – are designed for the general population; there are no specific guidelines for older adults. As a rule of thumb, metformin is recommended as the first-line therapy when lifestyle management fails to reach the treatment goal. Further intensification with dual therapy, triple therapy, or combination injectable therapy is also suggested when monotherapy fails, since combination therapy works more effectively and brings additional benefits to patients compared with monotherapy. Individualised care is promoted in the guidelines for selecting appropriate medications for patients, depending on drug efficacy and potential adverse effects such as hypoglycaemia, weight change, and cardiovascular and renal effects. The medications for type 2 diabetes, called antihyperglycemic or antidiabetic drugs, are summarised in Appendix A-1 according to the pharmacological mechanisms (Bailey and Kodack 2011; Peron, Ogbonna, and Donohoe 2015; ADA 2018; Joint Formulary Committee 2018).

In the latest version of the ADA guidelines, older adults are advised to undergo a detailed assessment in the medical, psychological, functional, and social geriatric domains to determine appropriate targets and therapeutic approaches. For those with multiple long-term conditions, cognitive impairment, or functional dependence, less stringent glycaemic targets (HbA1c < 8.0–8.5%, 64–69 mmol/mol) should be applied (ADA 2018). Screening for diabetic complications, geriatric syndromes, cognitive function, and depression is also recommended for older diabetes patients, helping to individualise diabetes management (ADA 2018). The NICE guidelines on diabetes management target adults aged 18 and older overall. Older adults who may need more assessments or have special considerations in clinical practice are not discussed

separately, although individualised care according to the guidelines emphasises multimorbidity and polypharmacy (NICE 2015).

Some antihyperglycemic medications have been reported to be riskier for older adults because of their pharmacological mechanisms or adverse effects (Peron, Ogbonna, and Donohoe 2015; Diabetes Canada Clinical Practice Guidelines Expert Committee et al. 2018). Falls are the most common concern for those taking medications that have a strong effect in reducing blood sugar levels, such as insulin and its analogues, meglitinides, and sulphonylureas (SUs). Other concerns for older people are fractures (with thiazolidinediones (TZDs)), weight loss (with metformin and glucagon-like peptide-1 (GLP-1) agonists), weight gain (with insulin and its analogues, meglitinides, SUs, and TZDs), cognitive impairment (with metformin), heart disease (with TZDs), and urinary incontinence (with sodium-glucose cotransporter-2 (SGLT-2) inhibitors) (Wedick et al. 2002; Singh, Loke, and Furberg 2007; Moore et al. 2013; Peron, Ogbonna, and Donohoe 2015; Diabetes Canada Clinical Practice Guidelines Expert Committee et al. 2018). These concerns about antihyperglycemic agents for older people may vary in different persons, emphasising the importance of patient-centred management. To summarise, an individualised approach to diabetes care is crucial for older adults to balance the pros and cons, but so far no concrete strategies have been developed for this vulnerable group of people.

1.4.3 Polypharmacy and diabetes in older adults

Two characteristics of diabetes contribute to a strong link to polypharmacy. First, diabetes tends to coexist with multiple long-term conditions (Xu, Mishra, and Jones 2017; Zghebi et al. 2020) and to lead to diabetic complications, resulting in multimorbidity. The second feature is diabetes treatment itself, where there is a

consensus to intensify the treatment with dual therapy if lifestyle management or monotherapy fails (NICE 2015; ADA 2018). Diabetes patients who have additional risk factors for atherosclerotic cardiovascular disease or who are aged 40 and over are also advised to take statins (lipid-lowering agents) (ADA 2018). These features are likely to bring about polypharmacy in people with diabetes. Diabetes and its complications therefore have been shown to be associated with polypharmacy (Veehof et al. 2000; Nobili et al. 2011; Kim et al. 2014; Strehblow, Smeikal, and Fasching 2014; Dwyer et al. 2016; Noale et al. 2016; Abolhassani et al. 2017; Lim et al. 2017; Vicinanza et al. 2018). However, little is known about how diabetes influences comorbidities and polypharmacy in older people. Only a few studies have investigated polypharmacy specifically in older diabetes patients (Gadsby et al. 2012; Papazafiropoulou et al. 2014; Noale et al. 2016; Ribeiro Da Silva et al. 2016; Yashkin et al. 2018), and none have compared polypharmacy between those with and without diabetes.

Therapies for diabetes and other long-term conditions may interact. For example, β blockers, primarily the non-cardioselective type, tend to mask the clinical symptoms of hypoglycaemia and can consequently lead to severe hypoglycaemia. Moreover, exposure to high doses of statins (Jones et al. 2017) or to atypical antipsychotics (Semenkovich et al. 2015) has been found to increase the risk of diabetes. In addition to treatments for diabetes and comorbidities, some characteristics of older adults may further complicate polypharmacy issues (Peron, Ogbonna, and Donohoe 2015; Health in Aging Foundation 2017). Reduced physical function and altered pharmacokinetics lead to uncertainty about adverse drug reactions and drug-drug interactions, which may perform differently from the general population or become more severe (Prentice and Jebb 2001; Wojtczak, Kasznicki, and Drzewoski 2017). Geriatric syndromes are

also a common issue and place additional burdens of conditions and medications on older people (Health in Aging Foundation 2017). Hence, older diabetes patients need comprehensive and individualised assessments in terms of disease management, polypharmacy issues, estimated life expectancy, and quality of life. To summarise, diabetes shows a close relationship with polypharmacy whereby many concerns may arise, but there is limited understanding of this phenomenon in older adults. Therefore, more studies are warranted to define the role of diabetes in the network of comorbidities, polypharmacy, and health outcomes for older adults.

1.5 Gaps in current research

There has been growing interest in polypharmacy, resulting in an increasing number of relevant studies. The literature review on polypharmacy among older adults presented in the previous section identified several gaps. First, a disparity in the prevalence of and risk factors for polypharmacy among older adults has been noted. Differences in the definitions of polypharmacy and the age ranges of older people result in varying prevalence rates. There have been a few studies based on nationally representative samples of older adults, which have found inconsistent effects of socio-demographic characteristics on polypharmacy. Slater et al. explored polypharmacy in ELSA, but they employed an ambiguous definition of polypharmacy and imprecise adjustments of self-reported long-term health conditions (Slater et al. 2018). The current evidence emphasises the necessity for a nationally representative study with comprehensive information on demographics, social and economic determinants, and physical and mental health factors. Second, diabetes has been regarded as the main contributor to polypharmacy, but only a few studies have targeted older diabetes

patients. Also, little is known about whether polypharmacy differs in older people with diabetes from those without diabetes, since no research making direct comparisons has been done. Third, polypharmacy has been linked to several adverse outcomes among older adults, such as frailty and reduced physical function; however, no clear results have been found for mortality. Studies on the effects of polypharmacy on all-cause mortality have shown inconsistent associations. Some have shown no association (Lu et al. 2015; Sganga et al. 2015; Gutierrez-Valencia et al. 2017); others have shown increased risk for older people (Wang et al. 2015; Romano-Lieber et al. 2019); some have shown decreased risk for older diabetes patients (Yashkin et al. 2018); one review showed mixed findings for community-dwelling older adults (Fried et al. 2014). The numerical-only definitions of polypharmacy widely used in the literature also make the results less persuasive, as do the cross-sectional study designs. Furthermore, no research has explored the relationship between polypharmacy and specific causes of death. Lastly, particular drug classes (e.g. anticholinergics and psychotropics) have been flagged in some studies, but very few studies have been done to investigate how specific combinations of medications influence older adults with polypharmacy. Given the gaps found in the literature, more investigations into polypharmacy-related issues and the role of diabetes among older adults are imperative.

1.6 Aims and objectives

My PhD research aimed to understand the phenomenon of polypharmacy, to study its risk factors, to investigate the health consequences of polypharmacy, and to determine the role of diabetes in polypharmacy among older adults, using a nationally

representative sample of older adults from private households in England: participants in ELSA. ELSA collects comprehensive information on social and health aspects, providing the opportunity to explore other risk factors for polypharmacy beyond health conditions, and to establish the relevance of polypharmacy among older adults in relation to a broad range of health issues. Laying emphasis on the role of diabetes in polypharmacy for older people, my research first identified cases of undiagnosed diabetes, which are regarded as at high risk of developing polypharmacy. This PhD research focused on four research objectives, each of which was addressed in a separate study. The objectives were:

1. To report the prevalence of diagnosed and undiagnosed diabetes between 2004 (Wave 2) and 2012 (Wave 6) and the risk factors for undiagnosed diabetes.
2. To investigate the prevalence of and risk factors for polypharmacy according to diabetes status (diagnosed and undiagnosed).
3. To study the association between different levels of polypharmacy and all-cause and cause-specific mortality.
4. To explore the association between high-risk medications and all-cause and cause-specific mortality among older adults with polypharmacy.

The four objectives were accompanied by four hypotheses:

1. It was hypothesised that the prevalence of undiagnosed diabetes had decreased over time, concomitant with improved awareness of diabetes resulting from the effort invested in both public information campaigns and screening tests in primary care in the UK over the period between 2004 and 2012.

2. It was hypothesised that diabetes contributed to the development of polypharmacy among older people, and that it might influence the potential risk factors for polypharmacy.
3. It was hypothesised that a gradient relationship existed between different levels of polypharmacy and all-cause and cause-specific mortality among older adults, independently of health status.
4. It was hypothesised that some high-risk medications might further increase the risk of mortality in older adults with polypharmacy.

Chapter 2. Data source: ELSA

2.1 Introduction to ELSA

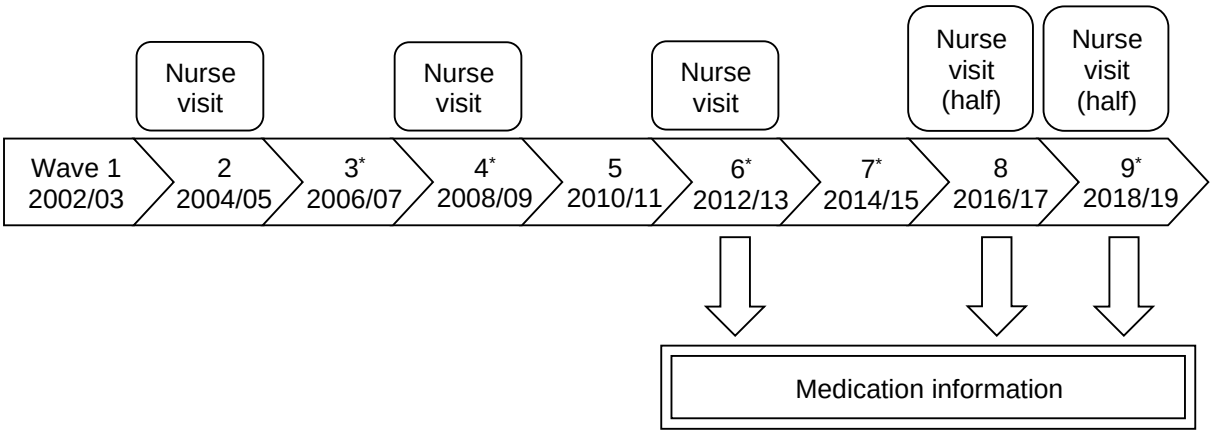
ELSA is an ongoing panel study of a nationally representative sample of adults in England aged 50 and older living in private households (Steptoe et al. 2013). ELSA began in 2002, and the original sample was drawn from respondents to the Health Survey for England between 1998 and 2001. At Waves 3, 4, 6, 7, and 9, the study was refreshed with new study participants (younger individuals) from the Health Survey for England to maintain the size and representativeness of the panel (aged 50 and older) (Institute for Fiscal Studies 2016; NatCen Social Research 2018). A graphical summary of ELSA is shown in Figure 2.1.

Data collection in ELSA is carried out every two years using computer-assisted personal interviews followed by self-completion questionnaires, and every four years through home visits from a study nurse during which biological samples and anthropometric measurements are taken (Bridges, Hussey, and Blake 2015; Institute for Fiscal Studies 2016). The nurse assessments were carried out on the whole core sample every four years in Waves 1–7, and on half the sample every two years from Wave 8 onwards. The response rates to the nurse interviews are high (greater than 83.8%), summarised in Table 2.1 (NatCen Social Research 2018). Many measures adopted in ELSA are comparable with those used in the US Health Retirement Study and the Survey of Health, Ageing and Retirement in Europe (NatCen Social Research 2018). The Wave 9 data, which is the most recent to date, is available from the UK Data Service. Information on changes in participants' health and economic and social circumstances is comprehensively collected in ELSA, helping researchers to

understand the picture of growing older in the 21st century and the reasons for the variety of patterns observed.

ELSA is administered by a team of researchers based at University College London, NatCen Social Research, the Institute for Fiscal Studies, and the University of Manchester. Other academic collaborators from the universities of Cambridge, Exeter, and East Anglia have provided expert advice on specific modules. Funding is provided by the US National Institute on Aging and by a consortium of British government departments coordinated by the National Institute for Health Research (NatCen Social Research 2018).

Figure 2.1 Graphical summary of ELSA



* Waves 3, 4, 6, 7, and 9 were refreshed with new study participants from the Health Survey for England.

Table 2.1 Response rates to nurse interviews by wave

	Eligible participants*	Productive participants#	Response rate
Wave 2 (2004–05)	8780	7666	87.3%
Wave 4 (2008–09)	9592	8218	85.7%
Wave 6 (2012–13)	9169	7730†	84.3%
Wave 8 (2016–17)	3714	3479	93.7%
Wave 9 (2018–19)	3640	3047	83.8%

* Core members who completed computer-assisted personal interviews.

Core members.

† 7731 in the document, corrected to 7730 based on the available nurse data from Wave 6.

2.2 Medication information in ELSA

Medication profiles were collected in Wave 6 (2012–13) for the first time, and will be collected during the main interview in future waves. A second set of complete information on medicines is provided by combining Wave 8 (2016–17) and Wave 9 (2018–19), because half of the sample was involved in the nurse visits for each wave. Coded data on medications is available from the Wave 6 nurse data and the Wave 8 and Wave 9 nurse special licence data set (NatCen Social Research 2018). All medications are recorded by the study nurses during home visits, and these medicines, both generic and branded, are transformed into codes based on the British National Formulary (BNF). Drug codes are summarised in the 'Coding prescribed medications' booklet, which includes information on the code frame for the drug-coding data (NatCen Social Research 2018).

During home visits, nurses ask participants whether they are taking or using any medicines, pills, syrups, ointments, puffers, or injections prescribed by a doctor or nurse. Then, participants are asked to show the containers for all the prescribed medicines currently being taken (NatCen Social Research 2018). Although the study

nurses intend to exclusively record prescribed medications, they cannot double-check prescriptions for medicines. Thus, the possibility of their recording OTC medicines cannot be ruled out completely. According to the questionnaire, nurses record OTC statins bought from a pharmacist (without a doctor's prescription) separately from prescribed statins, but 54 participants who had answered that they had bought statins without a prescription have the drug code for statins in the database. This situation may be attributed to not only prescribed medications being recorded, or to two or more statins being taken. The latter seems unlikely, because the concurrent use of two or more statins is not common where combination therapy with other lipid-lowering drugs is highly recommended (NICE 2019). Moreover, some prescribed medications, such as supplements, painkillers (e.g. paracetamol), and gastrointestinal medications (e.g. Fybogel for constipation), can also easily be bought over the counter. As a result, it is plausible to say that all medications, instead of only prescribed medications, are collected during nurse visits.

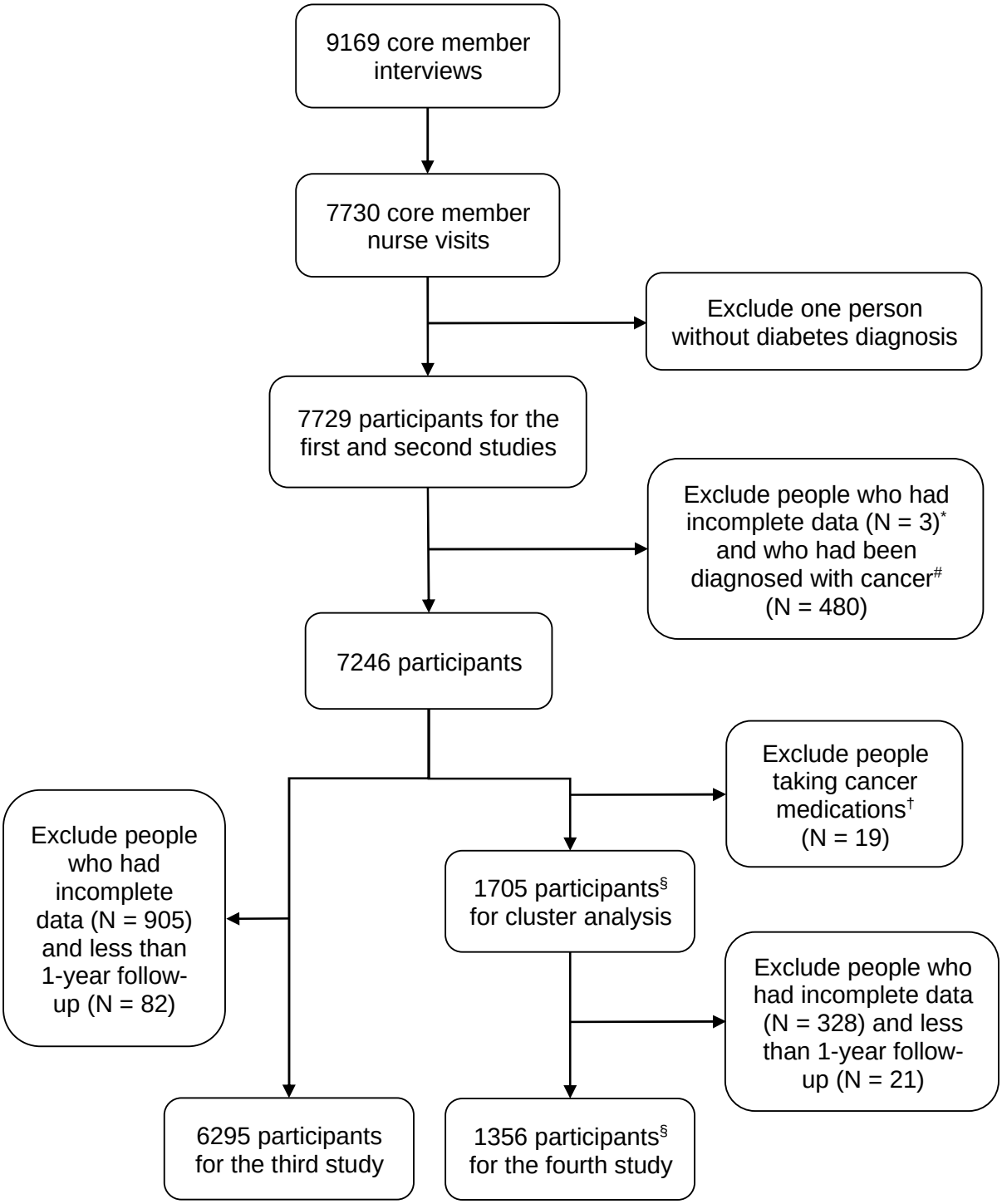
The analyses conducted for this PhD work were based on Wave 6 (2012–13), since this was the first wave containing medication information. The medications data from Wave 8 (2016–17) could not be used, because it was collected from only half of the original sample; the data from Wave 9 was released in late 2020, and therefore was not included in my PhD. In addition to Wave 6, Wave 2 (2004–05) was also used to explore changes in the prevalence of undiagnosed diabetes among older adults.

2.3 Study populations

This section summarises the study populations in each set of analysis carried out in this thesis. At Wave 6 of ELSA, 9169 core members completed personal interviews,

and 7730 of them also completed productive nurse visits, as shown in Figure 2.2. This PhD work comprised four studies, each addressing the objectives outlined in section 1.6. The first study aimed to analyse the prevalence of and risk factors for undiagnosed diabetes in a sample of 7729 participants from Wave 6, and compared this with data from 7666 individuals who took part in the Wave 2 nurse assessments and had information on diabetes diagnosis. The second study investigated the prevalence of and risk factors for polypharmacy according to diabetes status, and the sample size was the same as in the first study (7729 individuals from Wave 6). In the third study, the relationship between polypharmacy (measured in Wave 6) and subsequent mortality (up to 2018) was investigated using survival analysis. Participants who had been diagnosed with cancer or malignant blood disorders (N = 480), who had died within one year of follow-up (N = 82), or who had incomplete information regarding the variables in the model (N = 905) were excluded, resulting in 6295 participants included in the analysis. The fourth study further examined the association between medication use and mortality among older adults with polypharmacy, using a combination of cluster analysis and survival analysis. Apart from the exclusion of self-reported cancer and malignant blood disorders, 19 individuals on hormone therapy (primarily for cancers) were also excluded, resulting in 1705 participants with polypharmacy for the cluster analysis. Next, participants who had incomplete information regarding the variables in the model (N = 328) and who had died within one year of follow-up (N = 21) were excluded, so the analytical sample for the survival analysis was 1356 individuals.

Figure 2.2 Flow chart of study populations at Wave 6



* People without information on physical activity and functioning (N = 2) and follow-up time (N = 1).

Including cancer and malignant blood disorders self-reported by participants.

† Referring to hormone therapy that is primarily for cancers.

§ People with polypharmacy only.

Chapter 3. Undiagnosed diabetes in ELSA Wave 6: prevalence change (2004 to 2012) and risk factors

Abstract

Background

In light of recent publicity campaigns to raise awareness of diabetes, we investigated changes in the prevalence of diabetes and undiagnosed diabetes in adults aged 50 and older in England between 2004 and 2012, and explored risk factors for undiagnosed diabetes.

Method

7666 and 7729 individuals were from Wave 2 (2004–2005, mean age 66.6) and Wave 6 (2012–2013, mean age 67.6) of the ELSA. Diagnosed diabetes was defined as either self-reported diabetes or taking diabetic medications. Undiagnosed diabetes was defined as not self-reporting diabetes and not taking diabetic medications, but having a glycated haemoglobin measurement ≥ 48 mmol/mol (6.5%).

Results

There were increases in both diagnosed diabetes (7.7% to 11.5%) and undiagnosed diabetes (2.4% to 3.4%) between 2004 and 2012. However, a small decrease in the proportion of people with diabetes who were unaware of this condition (24.5% to 23.1%, $p < 0.05$) was observed. Only men aged 50–74 showed a stable prevalence of undiagnosed diabetes, with better recognition of diabetes. Age, non-white ethnicity, manual social class, higher diastolic blood pressure and cholesterol level were factors associated with higher risks of undiagnosed diabetes, whereas greater depressive symptoms were related to lower risks.

Conclusion

This study suggests that the greater awareness of diabetes in the population of England has not resulted in a decline in undiagnosed cases between 2004 and 2012. A greater focus on people from lower socioeconomic groups and those with cardiometabolic risk factors may help early diagnosis of diabetes for older adults.

This work was published in the *Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* (Huang, Steptoe, and Zaninotto 2021).

3.1 Background

Diabetes is a common long-term condition among older people worldwide, including in the UK, where the prevalence of doctor-diagnosed diabetes among people aged 65 and over rose from 5.6% in 1994 to 15% in 2017 (NHS Digital 2018). Diabetes is related to higher risks of all-cause and cause-specific mortality (Gregg et al. 2018), while the economic burdens, including healthcare and medical expenditures, are substantial (Dall et al. 2014).

Undiagnosed type 2 diabetes is frequent because of the asymptomatic features of the condition in its initial stage (WHO 2016). Diabetic complications such as retinopathy, neuropathy, and atherosclerotic lesions are common in people with newly diagnosed diabetes, indicating that the complications may have progressed prior to the diagnosis, during an undiagnosed phase of diabetes (Harris and Eastman 2000; WHO 2016; Diabetes Canada Clinical Practice Guidelines Expert Committee et al. 2018). Clinically, undiagnosed diabetes means that the diabetes is not monitored by health professionals, and blood sugar levels are not controlled properly. This situation

will speed up diabetic complications and subsequently lead to comorbidities and polypharmacy (WHO 2016). Therefore, cases of undiagnosed diabetes cannot be ignored and should be regarded as no less important than diagnosed cases. Before an assessment of the relationship between polypharmacy and diabetes is made, it is important to understand the scale of undiagnosed diabetes in the community.

When undiagnosed diabetes develops in older people, their health may be compromised (Taubert et al. 2003; Wild et al. 2005). The change in physical composition and the presence of comorbidities among older adults can make diagnosis difficult (Prentice and Jebb 2001); therefore, early diagnosis of diabetes is important, especially for older people, who may have comorbidities (Kirkman et al. 2012; Corriere, Rooparinesingh, and Kalyani 2013). To address this issue, a range of screening tools and risk assessment protocols have been developed in many countries (Hippisley-Cox et al. 2009; Dong et al. 2011; Li, Williams, and Douglass 2011; Zhang et al. 2014). Public health information about the dangers of diabetes has increased in recent years in various ways, including increased recognition of the links between unhealthy lifestyles and diabetes, campaigns to improve awareness, the introduction of an annual Diabetes Week in the UK, and the implementation of screening tests in primary care (Temelkova-Kurktschiev and Stefanov 2012; NHS 2019; Diabetes UK 2020). The NHS Health Check system, which targets people aged 40−74, was launched in 2009 (NHS 2019), and the system has been shown to detect more cases of diabetes, hypertension, and chronic kidney disease among attendees compared with non-attendees (Robson et al. 2017). One might therefore expect that rates of undiagnosed diabetes in England fell after this system was introduced.

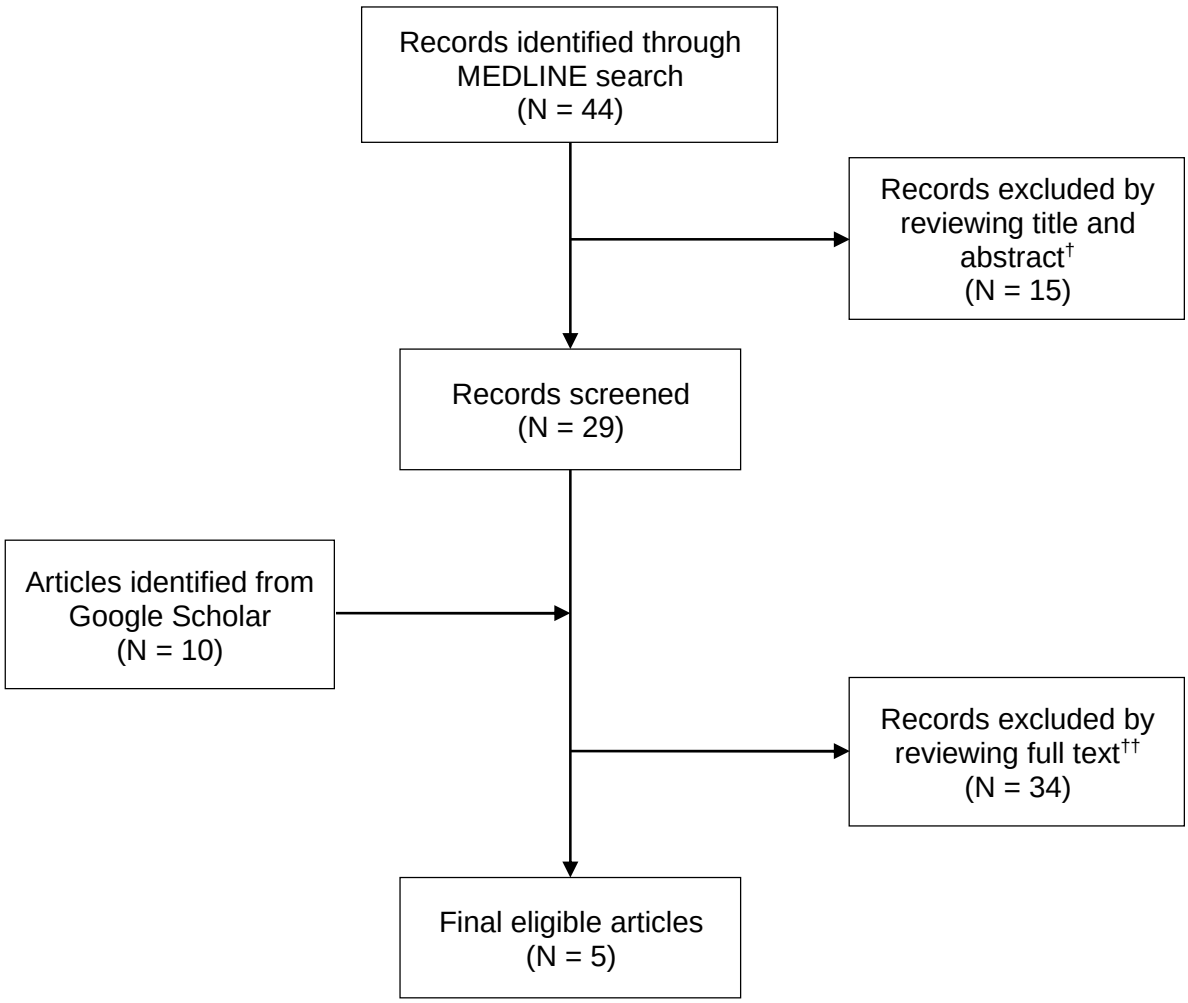
To understand the existing evidence, a literature search was carried out through the MEDLINE database using the search terms ‘diabetes mellitus or hyperglycaemia’,

‘undiagnosed’, ‘aged’, ‘prevalence’, and ‘risk factors’. Studies on the prevalence of or risk factors for undiagnosed diabetes in older people were included, and Figure 3.1 displays the literature review process. Studies of undiagnosed diabetes among older people were scarce and had applied different definitions, with a reported prevalence of between 0.9% and 13.2% (Harris and Eastman 2000; Dankner et al. 2009; Pierce et al. 2009; Leahy et al. 2015; Sinnott et al. 2015). Among these studies, three were based on people aged 50 and over, and they applied different criteria for undiagnosed diabetes (Dankner et al. 2009; Pierce et al. 2009; Leahy et al. 2015). Two of the three studies were based on nationally representative samples, in England (Pierce et al. 2009) and Ireland (Leahy et al. 2015) respectively. Pierce et al. also reported that 18.5% of diabetes cases in the older population were unaware of their condition (Pierce et al. 2009). To date, no consensus on risk factors for undiagnosed diabetes in older people has been reached, although male sex, age, rural locality, a lack of private healthcare insurance in some countries, good self-rated health, a family history of diabetes, the use of antihypertensive medicines, higher BMI, waist circumference (abdominal obesity), systolic blood pressure (SBP), triglyceride and low-density lipoprotein levels, and lower cholesterol levels have been reported to relate to a higher risk of undiagnosed diabetes among older people (Dankner et al. 2009; Pierce et al. 2009; Leahy et al. 2015; Sinnott et al. 2015). Furthermore, factors such as ethnicity, education level, and diastolic blood pressure (DBP) have been associated with undiagnosed diabetes in adults in general, although not specifically among older people (Hariri et al. 2006; Islam et al. 2016; Moody et al. 2016; Zhang et al. 2017). The prevalence of undiagnosed diabetes in adult populations also varies from 0.9% to 11.2%, with the proportion of unawareness between 23% and 55% (Hariri et al. 2006; Dall et al. 2014; Tamayo et al. 2014; Fisher-Hoch et al. 2015; Najafipour et al. 2015;

Islam et al. 2016; Meurs et al. 2016; Moody et al. 2016; Zhang et al. 2017). Differences in the prevalence and determinants of undiagnosed diabetes may be attributed to race, area, social background, diagnostic criteria for undiagnosed diabetes, and other factors (Harris and Eastman 2000; Hariri et al. 2006; Dankner et al. 2009; Pierce et al. 2009; Dall et al. 2014; Tamayo et al. 2014; Fisher-Hoch et al. 2015; Leahy et al. 2015; Najafipour et al. 2015; Sinnott et al. 2015; Islam et al. 2016; Meurs et al. 2016; Moody et al. 2016; Zhang et al. 2017).

The importance of early diagnosis of diabetes for older people is indisputable (Kirkman et al. 2012; Corriere, Rooparinesingh, and Kalyani 2013). To date, many studies have been based on adults across a wide age range (Hariri et al. 2006; Dall et al. 2014; Tamayo et al. 2014; Fisher-Hoch et al. 2015; Najafipour et al. 2015; Islam et al. 2016; Meurs et al. 2016; Moody et al. 2016; Zhang et al. 2017), or on non-representative samples (Chapin et al. 1999; Taubert et al. 2003; Mostaedi et al. 2014; Ursini et al. 2016); consequently, the generalisability of the results is limited. Little is known about whether the prevalence of and risk factors for undiagnosed diabetes in older people differ from those in younger adults. Also, the change in the prevalence of undiagnosed diabetes among older adults has not been explored over the last decade (Harris and Eastman 2000; Dankner et al. 2009; Pierce et al. 2009; Leahy et al. 2015; Sinnott et al. 2015). Therefore, this study aimed to investigate the prevalence of both diagnosed and undiagnosed diabetes between 2004 and 2012 in a nationally representative sample of older adults, and to determine the potential risk factors for undiagnosed diabetes.

Figure 3.1 Flow chart of literature review process for undiagnosed diabetes in older adults



† Criteria were irrelevance to undiagnosed diabetes, very small sample size, or case study/report.

†† Criteria were accessibility of full text in English and reporting of prevalence or risk factors/predictors for undiagnosed diabetes.

3.2 Methodology

3.2.1 Study population

The data came from Wave 2 (2004–05) and Wave 6 (2012–13) of ELSA. Medication profiles were collected for the first time during the Wave 6 nurse visits, when the study nurses recorded information about all medicines. The analytical samples for this study

consisted of 7666 individuals in Wave 2 and 7730 in Wave 6 who took part in the nurse assessments. Among these, 5816 out of 7666 in Wave 2 and 5813 out of 7730 in Wave 6 had valid HbA1c measurements. One case out of the 7730 in Wave 6 was excluded because there was no information on diabetes diagnosis. Among the participants in Wave 6, 4330 (56.0%) had also participated in Wave 2; the rest were from the new refreshment samples included in Waves 3, 4, and 6.

3.2.2 Outcome variables

The outcome variables used were diagnosed and undiagnosed diabetes. Diagnosed diabetes was defined as either self-reported doctor-diagnosed diabetes or the taking of diabetes medications (listed in Appendix B-1). Undiagnosed diabetes was defined as not having self-reported diabetes and any diabetic medications, but having an HbA1c measurement ≥ 48 mmol/mol (equivalent to 6.5% for the HbA1c measurement in 2004) (John 2012). The information on medications, which was available for 2012 only, helped to verify the quality of self-reported diabetes in this study.

3.2.3 Risk factors

Socio-demographic characteristics

Age (in years) was analysed as a continuous variable. Education was classified into ‘no qualifications’ and ‘some qualifications’ (primary, secondary, and college and above). Ethnicity was coded as white and non-white. Cohabitation was defined as living with a partner. Wealth was used as the measure of economic resources, since it is more consistently associated with health outcomes at older ages than income (Demakakos, Marmot, and Steptoe 2012). Wealth was computed from detailed

assessments of housing wealth, savings, investments, and possessions net of debt (Taylor et al. 2007; Crawford 2012). It was modelled as a continuous variable in the main analyses, but quintiles were presented for descriptive purposes. Occupational social class was defined according to current or most recent occupation, coded according to the national statistics socio-economic classification (known as NS-SEC), and further classified as professional-managerial or intermediate class versus manual social class. Education and occupational social class were coded as binary variables in order to make the results comparable with previous research (Pierce et al. 2009).

Health factors

Valid measurements obtained during nurse assessments for BMI, waist circumference, SBP, DBP, triglycerides, and total cholesterol were treated as potential risk factors in the analyses. Adiposity was ascertained from BMI and waist circumference and classified into 'normal BMI and waist circumference', 'high BMI and waist circumference', and 'either high BMI or high waist circumference'. High BMI was defined as BMI 30 and over. The cut-off values for waist circumference were 102 cm in males and 88 cm in females. The cut-offs of obesity for BMI and waist circumference were used because abdominal obesity and higher BMI have been identified as specific risk factors for undiagnosed diabetes in the literature. Self-reported hypertension, CVD, and hyperlipidaemia, considered to be potentially related to diabetes, were included in this study. Smoking status (i.e. whether a current smoker or not) was also investigated. Depression was defined as having four or more depressive symptoms assessed by the eight-item version of the Centre for Epidemiological Studies Depression Scale (CES-D) (Zivin et al. 2010). Cognitive function was assessed by

immediate and delayed recall memory tests. Participants were administered a list of 10 words orally, and then asked to recall as many words as possible. Recall was repeated after a five-minute delay. The word list comprised four different versions, so that different lists could be administered in different waves of the data collection. Scores derived from memory tests ranged from zero to 20.

3.2.4 Statistical analysis

The percentage of unawareness among people with diabetes was calculated by dividing the proportion of undiagnosed diabetes by the total amount of diabetes (undiagnosed plus diagnosed). Multivariable logistic regression was used to determine the risk factors significantly associated with undiagnosed diabetes. The variables were entered into the model simultaneously and included age (continuous), gender, education, ethnicity, cohabitation, total wealth (continuous), social class, obesity, SBP (continuous), DBP (continuous), triglycerides (continuous), total cholesterol (continuous), smoking status, cognitive function (continuous), self-reported hypertension and CVD, and depression. Statistical analyses were conducted using Stata (version 15.1; StataCorp LP, College Station, TX, USA).

Weighting

Inverse probability weighting was applied to adjust for sampling probabilities and differential non-responses in 2004 and 2012. Nurse weight was used for those who received nurse visits, and blood weight was used for those who also provided blood samples (Bridges, Hussey, and Blake 2015). The weighting was designed to render

the results representative of English people aged 50 and older living in private households in 2004 and 2012.

Sensitivity analysis

Several sensitivity analyses were carried out. First, fasting glucose ≥ 7 mmol/L was applied as the diagnostic criterion instead of HbA1c. Fasting glucose was only available for a subset of participants, so the sample size was reduced. Second, analyses were repeated using a stricter threshold for undiagnosed diabetes (HbA1c ≥ 53 mmol/mol (7%)). Third, since 4330 participants in the sample were present at both waves, longitudinal changes in diabetes prevalence among the same individuals were investigated. Lastly, to assess any potential bias due to missing HbA1c data in 2012, the characteristics of participants without diagnosed diabetes who had a nurse assessment and a valid HbA1c measurement (N = 5206) were compared with those who had a nurse assessment but missing HbA1c data (N = 1593).

3.3 Results

3.3.1 Prevalence of undiagnosed diabetes in 2004 and 2012

The characteristics of the study samples in 2004 and 2012 are summarised in Table 3.1. The mean age was 66.6 years in 2004 and 67.6 years in 2012, and the gender distribution was similar between the two waves, with 55% female and 45% male. Among the participants in 2004, 37.4% had no educational qualifications, while the proportion was 24.6% in 2012. Participants in 2004 showed increasing proportions from the lowest quintile of wealth to the highest quintile, whereas the proportions were similar across the quintiles in 2012. Also, the proportion of people with manual social

class backgrounds was slightly higher in 2004 than in 2012. Similar distributions were observed in the rest of the variables.

Table 3.1 Cohort characteristics in ELSA 2004 and 2012

	2004 (N = 7666) % (N)	2012 (N = 7729) % (N)
Age (years) mean ± SD	66.6 ± 9.9	67.6 ± 9.5
Gender		
Men	45.0 (3451)	44.6 (3447)
Women	55.0 (4215)	55.4 (4282)
Education		
No qualifications	37.4 (2862)	24.6 (1893)
Some qualifications	62.6 (4801)	75.4 (5802)
Ethnicity		
White	98.2 (7524)	96.9 (7493)
Non-white	1.8 (139)	3.1 (236)
Living with a partner	68.6 (5257)	67.9 (5250)
Total wealth		
1 (lowest)	16.9 (1276)	20.2 (1464)
2	19.5 (1478)	19.9 (1440)
3	20.5 (1547)	20.1 (1457)
4	21.1 (1596)	20.0 (1449)
5 (highest)	22.0 (1666)	19.7 (1428)
Social class based on occupation		
Professional-managerial or intermediate	56.7 (4282)	61.5 (4699)
Manual	43.3 (3268)	38.5 (2937)
Obesity		
High BMI and waist circumference	27.7 (1969)	28.3 (2188)
Either high BMI or high waist circumference	24.6 (1749)	22.4 (1734)
SBP (mmHg) mean ± SD	135.3 ± 18.9	132.2 ± 17.5
DBP (mmHg) mean ± SD	75.0 ± 11.2	73.5 ± 10.7
Triglyceride (mmol/L) mean ± SD	1.8 ± 1.2	1.5 ± 0.9
Cholesterol (mmol/L) mean ± SD	5.9 ± 1.2	5.5 ± 1.2
Current smoker	14.5 (1111)	11.5 (892)
Cognitive function mean ± SD	9.96 ± 3.6	10.7 ± 3.6
Hypertension	43.6 (3341)	40.2 (3105)
CVD	25.7 (1972)	24.2 (1870)
Hyperlipidaemia	–	38.8 (2995)
CES-D scores		
Less than 4	85.0 (6451)	86.8 (6639)
4 and above	15.0 (1136)	13.2 (1011)

There were 592 diagnosed and 115 undiagnosed (HbA1c ≥ 48 mmol/mol) cases in 2004, when no medications were collected. In 2012, only 890 participants reported having diabetes, but 930 diagnosed and 169 undiagnosed participants were identified after medications were taken into account. The difference in the number of undiagnosed cases before and after the verification of medication use in 2012 is summarised in Appendix B-2.

The overall prevalence of diagnosed and undiagnosed diabetes significantly increased from 2004 to 2012, while awareness of the condition among people with diabetes improved slightly (Table 3.2). However, changes in the prevalence of undiagnosed diabetes and diabetes unawareness differed by age and gender (Table 3.3).

Table 3.2 Prevalence of diagnosed and undiagnosed diabetes in England in 2004 and 2012

	2004		2012		Diff.
	%	95% CI*	%	95% CI*	*P*
Diagnosed diabetes#	7.7	7.1, 8.4	11.5	10.7, 12.3	**< 0.001**
Undiagnosed diabetes	2.4	2.0, 2.9	3.4	2.8, 4.0	**< 0.001**
Unawareness among diabetic people	24.5	23.5, 25.5	23.1	22.2, 24.0	**0.041**

* CI = confidence interval.

Weighted by non-response weight.

Table 3.3 Prevalence of diagnosed and undiagnosed diabetes by age and gender in England in 2004 and 2012

	Age 50-74		Diff.	Age 75+		Diff.
	2004	**2012**	***P***	**2004**	**2012**	***P***
Men						
Diagnosed diabetes[#] %	8.3	11.1	**0.001**	11.7	17.3	**0.002**
95% CI	(7.3, 9.4)	(9.9, 12.4)		(9.5, 14.3)	(14.7, 20.3)	
Case (N)	234	340		84	141	
Undiagnosed diabetes %	3.2	2.3	0.063	3.2	7.9	**0.001**
95% CI	(2.5, 4.2)	(1.7, 3.2)		(1.9, 5.4)	(5.5, 11.3)	
Case (N)	57	43		15	33	
Unawareness among diabetic people %	29.2%	17.3%	**< 0.001**	23.1%	35.9%	**< 0.001**
95% CI	(27.5, 30.9)	(15.9, 18.7)		(20.0, 26.2)	(32.6, 39.2)	
Women						
Diagnosed diabetes[#] %	5.5	9.2	**< 0.001**	9.7	16.0	**< 0.001**
95% CI	(4.7, 6.4)	(8.1, 10.6)		(8.0, 11.8)	(13.7, 18.5)	
Case (N)	176	285		98	164	
Undiagnosed diabetes %	1.5	3.0	**< 0.001**	2.2	4.9	**0.007**
95% CI	(1.0, 2.2)	(2.2, 4.0)		(1.2, 4.0)	(3.3, 7.4)	
Case (N)	30	64		13	29	
Unawareness among diabetic people %	21.8%	24.9%	**0.003**	20.1%	25.0%	**0.007**
95% CI	(20.4, 23.2)	(23.4, 26.4)		(17.6, 22.6)	(22.4, 27.6)	

[#] Weighted by non-response weight.

The prevalence of diagnosed diabetes showed a noticeable increase from 7.7% in 2004 to 11.5% in 2012 (Table 3.2). More men were diagnosed with diabetes than women in both 2004 and 2012, and also in different age groups, as displayed in Table 3.3. For both men and women, the increase in the prevalence of diagnosed diabetes was greater among people aged 75+ than those aged 50–74.

There was a significant rise in the prevalence of undiagnosed diabetes from 2.4% to 3.4% between 2004 and 2012; however, men aged 50–74 revealed an unchanged prevalence of undiagnosed diabetes over time (3.2% versus 2.3%, p=0.063). The prevalence of undiagnosed diabetes was at least two times higher in 2012 than in 2004 among men aged 75+ (7.9% versus 3.2%), women aged 50–74 (3.0% versus 1.5%), and women aged 75+ (4.9% versus 2.2%).

The overall proportion of people with diabetes who were unaware of the condition reduced slightly from 24.5% in 2004 to 23.1% in 2012 (p=0.041); however, this masked important age and gender differences. Men with diabetes aged 50–74 were more aware of the condition in 2012 than 2004 (unawareness proportions: 17.3% versus 29.2%), while other people with diabetes (older men and all women) were less aware of the condition in 2012, with the greatest increase in the proportion of unaware individuals among men aged 75+ (23.1% versus 35.9%).

3.3.2 Risk factors for undiagnosed diabetes

The associations between potential risk factors and undiagnosed diabetes in 2012 are summarised in Table 3.4. After all other factors were accounted for, per one year increase in age, a 5% increase in the risk of undiagnosed diabetes was observed. Also, per each unit increase in DBP (mmHg) and cholesterol level (mmol/L), the risk of undiagnosed diabetes increased by 1.08 and 2.31 times respectively. Non-white

older adults (odds ratio (OR) = 3.40) and those in a manual social class (OR = 1.98) had a higher risk of undiagnosed diabetes. By contrast, greater depressive symptoms were related to a lower risk (OR = 0.36). Gender, education, wealth, obesity, smoking, or cognitive function were not associated with undiagnosed diabetes after adjustments for other variables.

Table 3.4 Risk factors for undiagnosed diabetes in England in 2012

	Undiagnosed diabetes (N = 588)		
	OR*	95% CI	*P*
Age (years)#	1.053	1.017, 1.090	**0.004**
Female gender	1.385	0.837, 2.291	0.205
No educational qualifications	1.002	0.577, 1.742	0.994
Non-white ethnicity	3.397	1.398, 8.254	**0.007**
Living with a partner	0.767	0.453, 1.298	0.322
Total wealth§	1.055	0.869, 1.279	0.590
Manual social class	1.981	1.205, 3.257	**0.007**
Obesity			
High BMI and waist circumference	1.085	0.591, 1.992	0.794
Either high BMI or high waist circumference	0.865	0.444, 1.684	0.670
SBP (mmHg)#	0.985	0.968, 1.003	0.101
DBP (mmHg)#	1.077	1.045, 1.111	**< 0.001**
Triglyceride (mmol/L)#	0.811	0.649, 1.014	0.067
Cholesterol (mmol/L)#	2.307	1.818, 2.926	**< 0.001**
Current smoker	1.428	0.636, 3.204	0.388
Cognitive function#	0.989	0.920, 1.063	0.763
Hypertension	0.665	0.409, 1.082	0.100
CVD	1.625	0.970, 2.721	0.065
Hyperlipidaemia	0.656	0.411, 1.046	0.077
CES-D scores 4 and above	0.356	0.170, 0.745	**0.006**

* Unweighted odds ratio.

§ From lowest quintile to richest quintile.

Per one-unit increase.

3.3.3 Sensitivity analysis

A first sensitivity analysis, which involved fasting glucose as the measure of metabolic dysfunction, and a second, which employed a stricter threshold of HbA1c ≥ 53 mmol/mol (7%), were carried out to assess the robustness of the primary results. The findings are described in the appendices (Appendix B-3 to Appendix B-6). As shown in Appendices Appendix B-3 and Appendix B-5, the two analyses both found improved awareness among people with diabetes, as in the primary results. However, the prevalence of undiagnosed diabetes was relatively stable in the sensitivity analyses. It would appear to be difficult to compare age- and gender-specific changes in diabetes prevalence and the proportions of unawareness in these analyses with the main findings, due to the significant shrinkage of undiagnosed cases in the two sensitivity analyses.

The results of the longitudinal change in diabetes prevalence among the 4330 participants who were present in both waves are shown in Appendices Appendix B-7 and Appendix B-8. This cohort showed an increasing prevalence of diabetes over time, both diagnosed (6.2% in 2004 to 13.8% in 2012) and undiagnosed (1.9% in 2004 to 4.0% in 2012), but the cohort had a fairly stable proportion of people with diabetes who were unaware of the condition (23.8% in 2004 to 23.2% in 2012). The age- and gender-specific changes in diabetes prevalence and the percentages of unawareness were in line with the main findings.

The last sensitivity analysis was done to examine whether HbA1c availability in participants without diagnosed diabetes was related to the explanatory variables in the model assessing risk factors for undiagnosed diabetes. People without available HbA1c values tended to be older, have no educational qualifications, be non-white, live without a partner, be poorer, be in a manual social class, be obese, have lower

DBP and cognitive function, and have hypertension, CVD, and higher depression scores (Appendix B-9). The significant differences between those with and without HbA1c measurements might lead to the underestimation (e.g. age) or overestimation (e.g. DBP) of the risk factors identified in this study.

3.4 Discussion

3.4.1 Summary

From a nationally representative sample of older men and women in England, it was found that the prevalence of diagnosed and undiagnosed diabetes increased between 2004 and 2012. The prevalence of diagnosed diabetes increased over time among men and women in different age groups. In general, men were more likely than women to have diagnosed diabetes. However, this was not the case for undiagnosed diabetes. Men aged 50–74 had a stable prevalence of undiagnosed diabetes, with a significant decline in the proportion of people with diabetes who were unaware of their condition. On the other hand, men aged 75+ and all women showed an increasing prevalence of undiagnosed diabetes, with the proportion of people who were unaware of the condition growing from 2004 to 2012.

The increase in diabetes prevalence was primarily due to the increase in diagnosed diabetes, and the impact of gender differences in undiagnosed diabetes was relatively small. The rising prevalence of undiagnosed diabetes among men was limited to adults aged 75+, while women had a significant increase in undiagnosed diabetes in both age groups. These findings to some extent confirmed the impact of the NHS Health Check system, which was established in 2009 and targets people aged 40−74. Men aged under 75 had an unchanged prevalence of undiagnosed

diabetes, although there was a rising rate among all women. During this period, the proportion of people with diabetes who were not aware of their condition improved slightly, primarily because of greater awareness among men aged 50–74 years.

The robustness of the findings was largely confirmed in the sensitivity analyses. The only exception was that the prevalence of undiagnosed diabetes did not show an increase in the sensitivity analyses when fasting glucose and HbA1c of 7% were used. Due to many missing values for fasting glucose, this analysis had a reduced sample size, which in turn may have influenced its statistical power. For the analysis with a higher HbA1c threshold, it was fair that fewer cases of undiagnosed diabetes were identified. At any rate, it was confirmed that the prevalence of undiagnosed diabetes did not decrease between 2004 and 2012. Furthermore, the similar patterns of diabetes prevalence in the same cohort suggested that the increasing prevalence of diagnosed and undiagnosed diabetes may have resulted from multiple factors rather than from the ageing of the sample. Also, this cohort did not show a better awareness of diabetes, except for men aged 50–74 years, which was in line with the main findings, supporting the reliability of the results of the longitudinal study.

3.4.2 Comparison with existing literature

Prevalence

The prevalence of undiagnosed diabetes among people aged 50 and over varies widely across studies, from 0.9% in Ireland in 2009–11 to 13.2% in Israel in 2009 (Dankner et al. 2009; Leahy et al. 2015). An earlier analysis of ELSA data from 2004 (Pierce et al. 2009) reported a prevalence of 1.7%, compared with the 2.4% found in this study. The earlier study used a raised fasting glucose level to identify diabetes,

while the results of this study were based on HbA1c. This study was not able to use fasting glucose because of the large number of missing values and a lack of information about the duration of fasting in ELSA 2012. The different criteria for undiagnosed diabetes may have resulted in the varying prevalence levels.

Risk factors

A wide range of risk factors for undiagnosed diabetes among older adults have been reported (Dankner et al. 2009; Pierce et al. 2009; Leahy et al. 2015; Sinnott et al. 2015), but there is little agreement across studies. Male gender, obesity, SBP, triglyceride, and cholesterol (reverse effect) levels were consistently related to undiagnosed diabetes in two studies (Pierce et al. 2009; Sinnott et al. 2015), but these associations were not found in others (Dankner et al. 2009; Leahy et al. 2015). This study's finding of older age as a risk factor for undiagnosed diabetes is confirmed by previous research (Sinnott et al. 2015), whereas the associations with lipids observed in this study are different from those reported in previous studies (Pierce et al. 2009; Sinnott et al. 2015). In this study, higher cholesterol levels were related to undiagnosed diabetes, whereas lower cholesterol levels and higher triglyceride concentrations were identified as risk factors in earlier studies. The use of fasting samples to define diabetes in previous studies may have influenced the triglyceride estimates, since triglyceride levels would be higher in the non-fasting state (Nigam 2011). In addition, the findings regarding non-white ethnicity and higher DBP in this study are in line with literature that focuses on adults in general instead of older people in particular (Islam et al. 2016; Moody et al. 2016).

Two previous studies have found undiagnosed diabetes to be more common among men than women (Pierce et al. 2009; Sinnott et al. 2015), but this gender difference has not been observed in other work (Dankner et al. 2009; Leahy et al. 2015) or in this study. Other risk factors for undiagnosed diabetes identified in previous studies did not emerge in this study, including obesity. It should be noted that factors related to diagnosis are not fixed, but will vary according to the vigour with which diabetes detection is pursued. It is possible that the growing recognition of diabetes risk among men, and its relationship with obesity, mean that these variables are no longer risk factors for undiagnosed diabetes. This explanation is endorsed by Table 3.3, since men aged 50–74 showed an improvement in their awareness of diabetes.

Although diagnosed diabetes is known to be associated with lower socio-economic position (Diabetes UK 2010; Agardh et al. 2011) and depression (Diabetes UK 2010; Li et al. 2016; Olvera et al. 2016), associations with undiagnosed diabetes have not previously been documented. Lower socio-economic position may be related to less awareness of diabetes, while people with depressive symptoms may be more likely to have contact with health professionals, leading to more frequent diagnosis.

3.4.3 Undiagnosed diabetes based on HbA1c

HbA1c is a universal diagnostic tool for diabetes approved by the WHO, and it can avoid the day-to-day variability of plasma glucose levels and the inconvenience of fasting or performing an oral glucose tolerance test (WHO 2011). The convenience of HbA1c-based diagnosis, which was widely applied in the UK in 2011 (John 2012), may have contributed to more confirmed cases of diabetes, resulting in a higher prevalence of diabetes since 2011. Nevertheless, according to published data from the Health Survey for England, there was a steady increase rather than a surge in the prevalence

of diagnosed diabetes across 2011 (Appendix B-10) (NHS Digital 2018), which suggests that the adoption of HbA1c did not greatly influence prevalence rates. The data therefore supports the rationale of this study's two time points, 2004 (before 2011) and 2012 (after 2011). Furthermore, the use of HbA1c raises some concerns, since the ageing process involves increasing HbA1c values, which may influence diabetes diagnosis in older people (John 2012; Diabetes Canada Clinical Practice Guidelines Expert Committee et al. 2018). It has been proven that HbA1c-based diagnosis is modified by ethnicity and gender, and that it can show discrepancies with glucose-based diagnosis (Lipska et al. 2010; Diabetes Canada Clinical Practice Guidelines Expert Committee et al. 2018). However, the sensitivity analysis with fasting glucose showed similar prevalence levels, thereby helping to justify the use of HbA1c in this study.

3.4.4 Strengths and limitations

The strengths of this study included the use of a nationally representative sample of older people from a population-based longitudinal study, the verification of self-reported health conditions by objective assessments of medications, the inclusion of a comprehensive set of potential risk factors, the comparison of prevalence rates with two different measurements (HbA1c and fasting glucose), the comparison of prevalence of undiagnosed diabetes and proportions of unawareness with two different thresholds of HbA1c (6.5% and 7%), and the longitudinal change in prevalence rates in the same cohort. All analyses showed an increased prevalence of diagnosed diabetes and an improved awareness of diabetes from 2004 to 2012. This suggested that the results of this study were robust.

Some limitations to this study should be acknowledged. First, ELSA is a longitudinal ageing study, and participants receive feedback on their blood biomarkers. It is possible that individuals with high blood sugar levels in 2004 contacted their GPs and had diabetes diagnosed. If this was the case, it is likely to have decreased the prevalence of undiagnosed diabetes in 2012. Second, the use of a single HbA1c value may have led to imprecision, since at least two tests or symptoms are usually needed to make a diagnosis in clinical practice (WHO 2011; John 2012). Lastly, recall bias cannot be avoided completely, even though self-reported diabetes was verified by the presence of diabetes medications.

3.5 Conclusion

This study confirmed that diabetes rates are increasing in England, but it also suggested that the greater awareness of diabetes in the population has not resulted in a decline in undiagnosed cases. This analysis of risk factors suggested that a greater focus on individuals with lower socio-economic status and on people with other cardiometabolic risk factors might help with the identification of diabetes at an earlier stage. It is hoped that the findings of this study will encourage the identification of undiagnosed diabetes among older adults in clinical practice.

Chapter 4. Polypharmacy in ELSA Wave 6: prevalence and risk factors

Abstract

Aim

To study the association between diabetes and the prevalence of and risk factors for polypharmacy among adults aged 50 and older in England.

Methods

A cross-sectional study (2012–2013) of the ELSA. Polypharmacy was defined as taking 5–9 long-term medications a day and heightened polypharmacy as 10 or more. Diabetes included diagnosed and undiagnosed cases (glycated haemoglobin ≥ 6.5% (48 mmol/mol)).

Results

Of 7729 participants, 1100 people had diabetes and showed higher prevalence rates of polypharmacy (41.1% vs 14.8%) and heightened polypharmacy (5.8% vs 1.7%) than those without diabetes, even when antihyperglycemic medications were excluded. Risk factors for polypharmacy also differed according to diabetes status. Among people with diabetes, risk factors for polypharmacy and heightened polypharmacy were having more long-term conditions (relative risk ratio (RRR) = 1.86; 3.51) and being obese (RRR = 1.68; 3.68), while females were less likely to show polypharmacy (RRR = 0.51) and heightened polypharmacy (RRR = 0.51) than males. Older age (RRR = 1.04) was only related to polypharmacy among people without diabetes.

Conclusions

Adults with diabetes had higher prevalence rates of polypharmacy and heightened polypharmacy than those without diabetes, regardless of including antihyperglycemic drugs. Early detection of polypharmacy among older people with diabetes needs to focus on co-morbidities and obesity.

This work was published in *Diabetes Research and Clinical Practice* (Huang et al. 2021b).

4.1 Background

Diabetes is a common long-term condition among older adults. In England, 15% of people aged 65 and older reported having diabetes in 2017 (NHS Digital 2018). Diabetes and its complications have been shown to be associated with polypharmacy, which is also common in CVD, dyslipidaemia, gastrointestinal illnesses, and mental illnesses (Veehof et al. 2000; Nobili et al. 2011; Kim et al. 2014; Strehblow, Smeikal, and Fasching 2014; Dwyer et al. 2016; Noale et al. 2016; Abolhassani et al. 2017; Lim et al. 2017; Vicinanza et al. 2018; Tefera, Alemayehu, and Mekonnen 2020). The progression of diabetes and the guidelines for its treatment may link diabetes to the presence of polypharmacy. As diabetes progresses, microvascular and/or macrovascular complications appear. Inevitably, people with diabetes develop multimorbidity, which the WHO defines as the coexistence of two or more chronic conditions (Geneva: WHO 2016). Multimorbidity requires multiple medications or regimens and therefore brings about polypharmacy in this population (Fowler 2008). Moreover, both ADA in the US and NICE in the UK suggest intensification with additional medications when lifestyle management or monotherapy fail to reach an

individual’s treatment goals. These treatment guidelines increase the risk of developing polypharmacy among patients with diabetes. More importantly, the direct effects of ageing on metabolic regulation aggravate the underlying pathophysiology of type 2 diabetes in ageing populations (LeRoith et al. 2019). The occurrence of type 2 diabetes in older adults is a result of complex interactions among genetic, lifestyle, and ageing effects (Lee and Halter 2017). Ageing effects may also interact with diabetes to accelerate the progression of diabetes complications (LeRoith et al. 2019). Older adults with diabetes are therefore more likely to show polypharmacy.

Polypharmacy and multimorbidity are both prevalent among older adults (Geneva: WHO 2019, 2016). Polypharmacy intuitively refers to the concurrent use of multiple medications; however, no firm definition has been developed in clinical practice, as discussed in chapter 1, section 1.2. Three main ways to define polypharmacy have been identified in a systematic review (Masnoon et al. 2017), and the classification of polypharmacy into appropriate and problematic has been advocated by NICE (NICE 2017) and NHS England (NHS England and NHS Improvement 2019), beyond numerical definitions. This classification has been adopted in much polypharmacy research investigating PIMs/PIPs. Some tools have therefore been developed to identify PIMs/PIPs, such as the Beers criteria (By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel 2019) and STOPP criteria (O'Mahony et al. 2015), which can help to evaluate the appropriateness of polypharmacy. Nevertheless, the assessment of polypharmacy must be personalised, and it is often limited by data availability in population-based studies. In summary, the differences in polypharmacy definitions make current studies difficult to compare, so the influence and consequences of polypharmacy among older people are difficult to study.

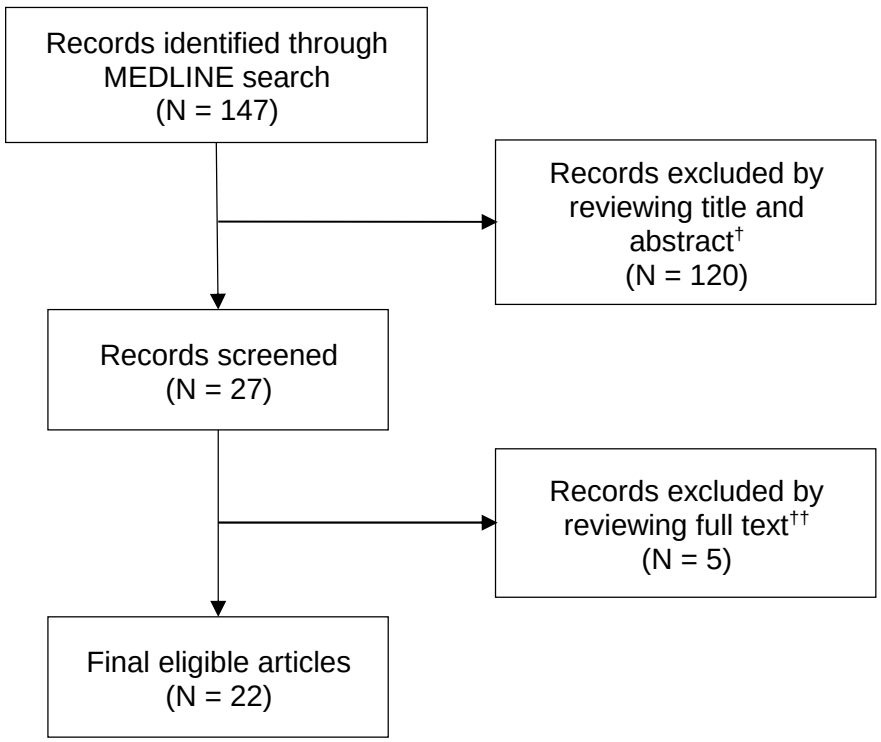
To understand the existing evidence, a literature search was carried out through the MEDLINE database using the search terms ‘polypharmacy’, ‘risk factors or factors’, and ‘aged’. Studies on the prevalence of and risk factors for polypharmacy in older people were included, and Figure 4.1 shows a flow chart of the literature review process. The prevalence of polypharmacy varies from 4% to 87.5% among older people when polypharmacy is defined as taking five or more drugs a day (Veehof et al. 2000; Brekke, Hunskaar, and Straand 2006; Nobili et al. 2011; Yong et al. 2012; Papazafiropoulou et al. 2014; Silveira, Dalastra, and Pagotto 2014; Strehblow, Smeikal, and Fasching 2014; Noale et al. 2016; Clague et al. 2017; Lim et al. 2017; Rawle et al. 2018; Slater et al. 2018; Vicinanza et al. 2018). Several factors have been reported to be associated with polypharmacy. These can be divided into two categories: socio-demographic characteristics such as age, gender, wealth, education, and ethnicity; and health factors, including the number of comorbidities, specific long-term conditions, obesity (BMI 30+), cognitive performance, malnutrition, and the use of supplements and oral antihyperglycemic drugs (Veehof et al. 2000; Cross, Wilson, and Binion 2005; Brekke, Hunskaar, and Straand 2006; Nobili et al. 2011; Yong et al. 2012; Kim et al. 2014; Papazafiropoulou et al. 2014; Silveira, Dalastra, and Pagotto 2014; Strehblow, Smeikal, and Fasching 2014; Dwyer et al. 2016; Noale et al. 2016; Abolhassani et al. 2017; Lim et al. 2017; Guaraldi et al. 2018; Komiya et al. 2018; Ong et al. 2018; Rawle et al. 2018; Slater et al. 2018; Vicinanza et al. 2018; Tefera, Alemayehu, and Mekonnen 2020). Factors that have been consistently reported as associated with a high risk of polypharmacy are older age and an increasing number of comorbidities (Veehof et al. 2000; Cross, Wilson, and Binion 2005; Yong et al. 2012; Kim et al. 2014; Papazafiropoulou et al. 2014; Silveira, Dalastra, and Pagotto 2014; Noale et al. 2016; Abolhassani et al. 2017; Lim et al.

2017; Guaraldi et al. 2018; Ong et al. 2018; Rawle et al. 2018; Slater et al. 2018; Vicinanza et al. 2018; Tefera, Alemayehu, and Mekonnen 2020). To date, only a few studies have focused on older adults with diabetes and reported a high prevalence of polypharmacy: 84% (Gadsby et al. 2012) for a cut-off of four; 57.1% (Noale et al. 2016) and 66% (Ribeiro Da Silva et al. 2016) for a cut-off of five; and 79% for a cut-off of six (Papazafiropoulou et al. 2014). Some studies have employed non-representative study samples in terms of specific long-term conditions and particular healthcare settings (Cross, Wilson, and Binion 2005; Nobili et al. 2011; Yong et al. 2012; Strehblow, Smeikal, and Fasching 2014; Dwyer et al. 2016; Clague et al. 2017; Guaraldi et al. 2018; Tefera, Alemayehu, and Mekonnen 2020). Population-based studies have applied various definitions of polypharmacy and different adjustments for long-term illness (Veehof et al. 2000; Brekke, Hunskaar, and Straand 2006; Kim et al. 2014; Silveira, Dalastra, and Pagotto 2014; Abolhassani et al. 2017; Lim et al. 2017; Komiya et al. 2018; Ong et al. 2018; Rawle et al. 2018; Slater et al. 2018; Vicinanza et al. 2018). All these differences among studies make it difficult to compare the results and generalise them to the older population. Also, little is known as to whether polypharmacy in people with diabetes is different from polypharmacy in people without diabetes.

Some polypharmacy is a legitimate response to multimorbidity and patient management according to clinical treatment guidelines. However, the recommendation to deprescribe for people with limited life expectancy (Maddison, Fisher, and Johnston 2011) has been increasingly endorsed. As a result of evidence of the positive and negative consequences of polypharmacy (Huang et al. 2010; Niikawa et al. 2017; Yashkin et al. 2018), there has been increasing debate about the rationale for polypharmacy, especially among older adults. Diabetes is one of the long-

term conditions that have been identified as implicated in polypharmacy. However, to date, no studies have evaluated the prevalence of or risk factors for polypharmacy between people with and without diabetes. Therefore, this study aimed to disentangle the role of diabetes in polypharmacy by studying the prevalence of and risk factors for polypharmacy in a nationally representative sample of older adults, according to diabetes status. Diabetes in this study included both diagnosed and undiagnosed cases, which had been identified in the previous study (chapter 3). It was hypothesised that diabetes contributed to the development of polypharmacy among older people and might influence the potential risk factors for polypharmacy.

Figure 4.1 Flow chart of literature review process for risk factors for polypharmacy



† Criteria were irrelevance to polypharmacy, very small sample size, case study/report, and pharmaceutical publications about specific medications.

†† Criteria were accessibility of full text in English and exploration of risk factors/predictors for polypharmacy.

4.2 Methodology

4.2.1 Study population

In Wave 6 of ELSA, a total of 9169 interviews with core members were conducted. Of these, 7730 participants were visited by a study nurse, who recorded information on all medications. This was the first time that this data had been collected in ELSA. The analytical sample for this study consisted of 7729 individuals who took part in the nurse assessments and had valid information regarding their diabetes diagnosis.

4.2.2 Polypharmacy

There is no consensus on the definition of polypharmacy, as discussed in chapter 1, section 1.2. Nevertheless, some characteristics are essential to polypharmacy and contribute to its rigorous definition. The key characteristics are the appropriate cut-off value of concurrent medications, exclusive long-term use, the inclusion of regularly used OTC drugs, and the calculation of active components in combination drugs. To make the results comparable with the literature, the most common cut-off values − five and 10 − were chosen to distinguish different levels of polypharmacy (Yong et al. 2012; Masnoon et al. 2017). Therefore, polypharmacy was defined as taking between five and nine long-term medications a day; taking 10 or more medications a day was defined as heightened polypharmacy. Long-term medications were either drugs for long-term conditions, such as antihyperglycemic and antihypertensive agents, or drugs for long-term symptoms, such as sedatives for insomnia and relievers for tremor (Huang et al. 2010; Papazafiropoulou et al. 2014; Masnoon et al. 2017). All the medication categories in long-term use are listed in Table 4.1. The included categories

were oral medicines, injections, inhalers, all forms of nicotine replacement, and nitroglycerine sublingual spray; non-oral medicines, premedication or post-operative drugs, and medications that could not be coded were excluded. Some medications were in short-term use most of the time and thus excluded from the study, including emergency contraceptives, drugs for febrile convulsion, painkillers (paracetamol-based), gastrointestinal medications (except for H_2-receptor blockers, prostaglandin E1 analogue, and proton-pump inhibitors), symptom-relieving drugs (e.g. for constipation, allergy, vertigo, cough, nausea, diarrhoea, and erectile dysfunction), medicines for infection (antibiotics, antifungals, and antivirals), and supplements. Furthermore, OTC drugs used for long-term conditions were also included in this study – for example, calcium supplements taken by older adults with bone disease. Each distinct pharmacological agent was treated as an individual drug, although a few combination drugs are indistinguishable in ELSA: for example, a combination of ARB and CCB has the same code as a single ARB. Distinguishable combination drugs are listed in Table 4.2 and were counted as two or three medications. In addition, polypharmacy excluding antihyperglycemic drugs and heightened polypharmacy excluding antihyperglycemic drugs were also adopted for people with diabetes.

Table 4.1 Medication categories in long-term use, ELSA 2012

Long-term condition	Medication category
Diabetes	Insulin, SUs, biguanides (metformin), dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, TZDs, GLP-1 agonists, α-glucosidase inhibitor, and SGLT-2 inhibitors
Diabetic neuropathy	Codeine and carbamazepine
CVDs	Digoxin, diuretics (thiazide, loop, potassium-sparing and combinations), antiarrhythmics, β blockers, α2 agonists, α1 blockers, CCBs, renin-angiotensin-aldosterone system (RAAS) inhibitors (ACEIs, ARBs, and renin inhibitors), vasodilators, and antithrombotics (anticoagulants and anti-platelets)
Hyperlipidaemia	Statins, fibrates, niacin, bile acid sequestrants, omega-3 fatty acids, cholesterol absorption inhibitors, and microsomal triglyceride transfer protein inhibitors
Hyperuricemia (including gout)	Allopurinol and NSAIDs (for acute attack)
Lung disease (including inhalers)	Steroids (oral and inhaled), β2 agonists (including long-acting), anticholinergics, theophylline, aminophylline, combinations (e.g. ipratropium plus salbutamol), mast cell stabilisers, and leukotriene receptor antagonists
Bone disease	Bisphosphonates
Psychiatric conditions	Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), typical antipsychotics, atypical antipsychotics, antimanic agents, and anxiolytics
Epilepsy (seizure)	Anticonvulsants, BZDs, and phenytoin
Parkinson's disease	Carbidopa-levodopa and anticholinergic (procyclidine)
Dementia (including Alzheimer's disease)	Acetylcholinesterase inhibitor (donepezil) and glutamate receptor antagonist (memantine)
Inflammatory bowel disease	Metronidazole, sulfasalazine, mesalazine, steroids, and immunosuppressants
Autoimmune disease (rheumatic disease, myasthenia gravis)	Steroids and immunosuppressants
Cancer	Immunosuppressants, steroids, oral chemotherapy, methotrexate, hormones, selective oestrogen receptor modulators, aromatase inhibitors, and gonadotropin-releasing hormone agonists

Table 4.1 (continued)

Long-term symptom	Medication category
Hormone therapy	Thyroxine (levothyroxine), steroids, sex hormones (including patches), gonadotropin-releasing hormone agonists, and contraceptives (not including emergency contraceptives)
Treatment for substance dependence (including alcohol, opioids, and smoking)	Including all forms of nicotine replacement therapy
Sedative (hypnotic)	BZD and non-BZD derivatives
Tremor	Propranolol
Symptom relief for pain, inflammation, and rheumatic disease	NSAIDs (including aspirin)
Pain relief	Opioid derivatives, and drugs for trigeminal neuralgia and migraine (including headache)
Peptic ulcers and gastroesophageal reflux disease	H_2-receptor blockers, prostaglandin E1 analogue, and proton-pump inhibitors
Supplements for people with bone disease	Calcium products
Attention deficit hyperactivity disorder	Methylphenidate
Tourette's syndrome	Sulpiride
Benign prostatic hyperplasia	5α reductase inhibitors and α1 blockers
Urinary incontinence	Anticholinergics (oxybutynin) and antimuscarinics (trospium chloride and solifenacin)
Urine alkalinisation, ureteric colic	Sodium bicarbonate and diclofenac
Thyrotoxicosis	Propranolol
Nocturnal cramps	Muscle relaxants (quinine, diazepam, and baclofen)
Dry mouth	Pilocarpine
Sputum viscosity	Carbocisteine

Table 4.2 Distinguishable combination drugs, ELSA 2012

Code	Combination drug
02.02.04	Potassium-sparing diuretic and another type of diuretics
03.01.04	Ipratropium and β2 agonist (inhaler)
07.03.01	Contraceptive, combined type
09.06.04	Calcium and vitamin D3

4.2.3 Risk factors

Socio-demographic characteristics

Age was modelled as a continuous variable. Binary variables were employed for gender (males and females), ethnicity (white and non-white), education (no qualifications versus some qualifications), occupational social class (intermediate/professional-managerial versus manual), and cohabiting status (living or not with a partner). Wealth was used as the measure of economic resources, since it is more consistently associated with health outcomes at older ages than income (Demakakos, Marmot, and Steptoe 2012). Wealth was computed from detailed assessments of housing wealth, savings, investments, and possessions net of debt. It was presented as quintiles from poorest to richest.

Comorbidity

Long-term conditions in ELSA Wave 6 were either self-reported by participants or determined by specific treatments. The self-reported diagnoses recorded in ELSA were diabetes, hypertension, angina (chest pain), heart attack, congestive heart failure, heart murmur, abnormal heart rhythm, stroke, other heart diseases, high cholesterol, lung disease, asthma, arthritis, osteoporosis, cancer, blood disorder (malignant), Parkinson's disease, Alzheimer's disease, dementia (including senility

and serious memory impairment), psychiatric conditions, and four eye diseases (glaucoma, diabetic eye disease, macular degeneration, and cataracts). To simplify the cardiovascular conditions, angina and heart attack were combined into ‘coronary heart disease (CHD)’; congestive heart failure, heart murmur, abnormal heart rhythm, and other heart diseases were combined into ‘other heart problems’. The diagnoses of hypertension and stroke remained independent. A new binary variable of CVD was generated to refer to participants who had reported any diagnosis of stroke, CHD, or other heart problems.

The self-reported long-term conditions were verified by medication profiles wherever possible. To reduce potential misclassification bias and recall bias in this study, both the participants who had self-reported and those who took medications were categorised as having a particular illness, and this was referred to as a verified diagnosis. The crude and verified diagnoses in ELSA 2012 are summarised in Table 4.3. Most of the diagnoses could be verified by the participant’s taking specific medication classes, and a broader diagnosis was accordingly established. For example, people with lung disease or asthma usually have similar prescriptions, so the two separate self-reported conditions were verified by medications and combined into ‘lung disease and asthma’. The verified diabetes diagnosis included not only diagnosed but also undiagnosed diabetes, building upon previous work (chapter 3). However, some diagnoses could not be verified in the same way, because cardiovascular medications (e.g. β blockers and ARBs) can be used for hypertension, heart failure, or other illnesses. The same situation applied to the use of lipid-lowering agents. Thus, the diagnoses of CVD, hyperlipidaemia, CHD, stroke, and other heart problems remained self-reported instead of verified. Accordingly, 10.2% of people were found to be taking cardiovascular medications or lipid-lowering agents but not

self-reporting relevant diagnoses (i.e. hyperlipidaemia, hypertension, or CVD). An indicator of inconsistency between medication use and self-reported conditions was therefore generated to refer to this group of people.

In addition to the self-reported conditions, four diagnoses – hyperuricemia (including gout), epilepsy (seizure), inflammatory bowel disease, and autoimmune disease (including rheumatic disease and myasthenia gravis) – were identified by recognisably specific treatments. The cases and prevalence of the four conditions were 193 (2.5%) for hyperuricemia, 181 (2.3%) for epilepsy, 47 (0.6%) for inflammatory bowel disease, and 158 (2.0%) for autoimmune disease.

The number of long-term conditions was derived from self-reported diagnoses and specific treatments. Sixteen diagnoses were included to generate the number of conditions (from zero to 16): hypertension, stroke, CHD, other heart problems, hyperlipidaemia, lung disease and asthma, arthritis, bone disease (including osteoporosis, Paget's disease, and heterotopic ossification), cancer and malignant blood disorder, Parkinson's disease, dementia (including Alzheimer's disease), psychiatric conditions, any one of four eye diseases, hyperuricemia, epilepsy, and inflammatory bowel disease. Diabetes (both diagnosed and undiagnosed) was excluded from the calculation due to the stratification by diabetes status in the subsequent analyses. Autoimmune disease defined by specific treatments was also excluded, since self-reported arthritis may refer to osteoarthritis or rheumatoid arthritis, which is also a type of autoimmune disease. Moreover, only a small number of people with autoimmune disease (23 out of 158) did not concurrently report arthritis, helping to justify the exclusion of autoimmune disease in this study.

Table 4.3 Crude and verified diagnoses, ELSA 2012 (N = 7729)

Self-reported diagnosis	N (%)	On drug, N / diagnosis, N (%)	On drug, N / no diagnosis, N (%)	Verified diagnosis	N (%)	On drug, N / diagnosis, N (%)
Diabetes	890 (11.5)	638/890 (71.7)	44/6839 (0.6)	Diabetes[#]	1100 (14.2)	682/1100 (62.0)
Hyperlipidaemia	2995 (38.8)	2010/2995 (67.1)	641/4734 (13.5)	Taking cardiovascular or lipid-lowering agents without a diagnosis	788 (10.2)	
Hypertension	3105 (40.2)	2753/3105 (88.7)	409/3819 (10.7)			
CVD[#]	1870 (24.2)	1550/1870 (82.9)				
Stroke	373 (4.8)	–	–			
CHD	785 (10.2)	–	–			
Other heart problems	1210 (15.7)	–	–			
Lung disease[†]	405 (5.2)	270/405 (66.7)	199/6602 (3.0)	Lung disease and asthma[§]	1325 (17.1)	1001/1325 (75.5)
Asthma[†]	877 (11.4)	671/877 (76.5)				
Arthritis[†]	3145 (40.7)	–	–			
Osteoporosis[†]	675 (8.7)	197/675 (29.2)	97/7053 (1.4)	Bone disease[#]	772 (10.0)	294/772 (38.1)
Cancer[†]	431 (5.6)	72/431 (16.7)[*]	35/7247 (0.5)[**]	Cancer and malignant blood disorder[**]	481 (6.2)	73/481 (15.2)
Blood disorder (malignant)[†]	58 (0.8)	4/58 (6.9)[*]				
Parkinson's disease[†]	47 (0.6)	35/47 (74.5)	28/7681 (0.4)	Parkinson's disease	75 (1.0)	63/75 (84.0)
Alzheimer's disease[†]	12 (0.2)	9/12 (75.0)	4/7660 (0.05)	Dementia (including Alzheimer's disease)[§]	72 (0.9)	19/72 (26.4)
Dementia[†]	61 (0.8)	10/61 (16.4)				

Table 4.3 (continued)

Self-reported diagnosis	N (%)	On drug, N / diagnosis, N (%)	On drug, N / no diagnosis, N (%)	Verified diagnosis	N (%)	On drug, N / diagnosis, N (%)
Psychiatric conditions[†]	863 (11.2)	401/863 (46.5)	510/6865 (7.4)	Psychiatric conditions	1373 (17.8)	911/1373 (66.4)
Eye: glaucoma[††]	503 (6.5)	–	–	Any 1 of 4 eye diseases[††]	2475 (32.0)	
Eye: diabetic eye disease[††]	177 (2.3)	–	–			
Eye: macular degeneration[††]	345 (4.5)	–	–			
Eye: cataract[††]	1940 (25.1)	–	–			

[†] One missing value in self-reported diagnoses.

[††] Five missing values in glaucoma; four missing values in macular degeneration; three missing values in diabetic eye disease, cataract, and combined diagnosis.

[*] Not including intravenous chemotherapy.

[**] Drugs for immunosuppression and cancer shared similar codes that sometimes were indistinguishable; thus, verified diagnosis did not take medications into account.

[#] Diabetes included diagnosed and undiagnosed cases. CVD included stroke, CHD, and other heart problems. Bone disease included osteoporosis, Paget's disease, and heterotopic ossification.

[§] People with a verified diagnosis were fewer than the sum of participants who self-reported and who were on medications but without corresponding diagnoses. This was because a small number of people had two self-reported conditions simultaneously when the verified diagnosis referred to a combination of the two diagnoses.

Other health factors

This study included health factors that had been reported in the literature and about which information was provided in ELSA, such as smoking status, obesity, and cognitive performance. Depressive symptoms, which had never been reported before, are related to diabetes and showed significance in the univariable analysis; therefore, they were included in this study. Smoking status was coded as current smoker or not. Frequency of alcohol consumption was classified as ‘daily (five to seven days per week)’ and ‘less than daily’. Obesity was derived from BMI and waist circumference, and categorised into ‘normal BMI and waist circumference’, ‘high BMI and waist circumference’, and ‘either high BMI or high waist circumference’. High BMI was defined as BMI 30 and over. The cut-off values for waist circumference were 102 cm in males and 88 cm in females. Depressive symptoms and cognitive function were also included in the study. Depressive symptoms were assessed by the eight-item version of the CES-D (Zivin et al. 2010), and total scores were used (ranging from zero to eight). Cognitive function was assessed using a memory test. Participants were administered a list of 10 words orally, and then asked to recall as many words as possible. Recall was repeated after a five-minute delay. Scores derived from immediate and delayed recall ranged from zero to 20.

4.2.4 Statistical analysis

For the descriptive analyses of long-term medications and conditions, the relationship between the two variables in the original scales was tested using Pearson correlation coefficient. Two-sample t-tests were used to examine the difference in continuous variables between two independent groups, and chi-square tests were employed to

explore the associations between categorical variables. The significance level was set to be less than 0.05.

Analyses of polypharmacy prevalence were weighted by inverse probability weighting to adjust for sampling probabilities and differential non-responses to the nurse visit in 2012 (Bridges, Hussey, and Blake 2015). The weighting was designed to render the results representative of adults in England aged 50 and older living in private households in 2012 (Wave 6).

Multinomial logistic regression was used to determine the risk factors associated with polypharmacy, in which zero to four medications was the reference group, and five to nine and 10 or more medications referred to different levels of polypharmacy. Relative risk ratios (RRRs), and corresponding 95% CIs, were reported to indicate the risk of the outcome being present in the comparison group relative to the reference group, conditional on fixed covariates in the model. The variables were entered into the model simultaneously and included age, gender, ethnicity, total wealth, education, social class, cohabitation status, number of conditions (excluding diabetes), smoking status, alcohol consumption, obesity, depressive symptoms, and cognitive function. Interaction terms were identified by likelihood ratio tests, a statistical test of the goodness-of-fit between two models (model being tested versus full model including interaction terms). Statistical analyses were conducted using Stata (version 15.1; StataCorp LP, College Station, TX, USA).

Sensitivity analysis

Sensitivity analyses were performed to check the robustness of results when employing specific long-term conditions plus the number of remaining conditions

instead of the sum of all conditions. Hypertension, hyperlipidaemia, and psychiatric conditions were adjusted individually as dichotomous variables, and a continuous variable of CVD referring to the number of CVDs was employed. The remaining conditions were combined into an illness count.

4.3 Results

First, this section introduces the characteristics of the study sample. Then a full description of medications collected in ELSA 2012 and the association between diabetes and medication use and comorbidities is given, followed by the prevalence of polypharmacy and heightened polypharmacy, and risk factors for the two levels of polypharmacy.

A total of 7729 participants (1100 with diabetes and 6629 without diabetes) were included in this study, and the characteristics of participants are summarised in Table 4.4. People with diabetes tended to have more long-term conditions, be older, be men, be non-white, be poorer, lack educational qualifications, be in a manual social class, live without a partner, drink less than daily, be obese, have worse cognitive performance, and have greater depressive symptoms.

Table 4.4 Cohort characteristics in ELSA 2012, stratified by diabetes

	No diabetes (N = 6629) % (N)	Diabetes (N = 1100) % (N)	*P*
Age (years) mean (SD*)	67.2 (9.5)	70.0 (9.1)	**< 0.001**
Gender			
Men	43.6 (2889)	50.7 (558)	**< 0.001**
Women	56.4 (3740)	49.3 (542)	
Ethnicity			
White	97.5 (6464)	93.5 (1029)	**< 0.001**
Non-white	2.5 (165)	6.5 (71)	
Total wealth			
1 (lowest)	19.0 (1187)	27.5 (277)	**< 0.001**
2	19.3 (1203)	23.6 (237)	
3	20.0 (1247)	20.9 (210)	
4	20.8 (1294)	15.4 (155)	
5 (highest)	20.9 (1301)	12.6 (127)	
Education			
No qualifications	23.3 (1543)	32.2 (350)	**< 0.001**
Some qualifications	76.7 (5064)	67.8 (738)	
Social class based on occupation			
Manual	37.0 (2426)	47.3 (511)	**< 0.001**
Intermediate or professional-managerial	63.0 (4129)	52.7 (570)	
Living with a partner			
Yes	69.0 (4572)	61.6 (678)	**< 0.001**
No	31.0 (2057)	38.4 (422)	
Number of conditions # median (IQR*)	2 (2)	3 (3)	**< 0.001**
Current smoker			
Yes	11.4 (753)	12.6 (139)	0.220
No	88.6 (5876)	87.4 (961)	
Alcohol consumption			
Less than daily	78.1 (4715)	86.4 (834)	**< 0.001**
Daily (5−7 days per week)	21.9 (1319)	13.6 (131)	
Obesity			
High BMI and waist circumference	26.4 (1664)	52.7 (524)	**< 0.001**
Either high BMI or high waist circumference	23.5 (1480)	25.6 (254)	
Cognitive function mean (SD)	10.9 (3.6)	9.7 (3.8)	**< 0.001**
Number of depressive symptoms mean (SD)	1.3 (1.8)	1.8 (2.1)	**< 0.001**

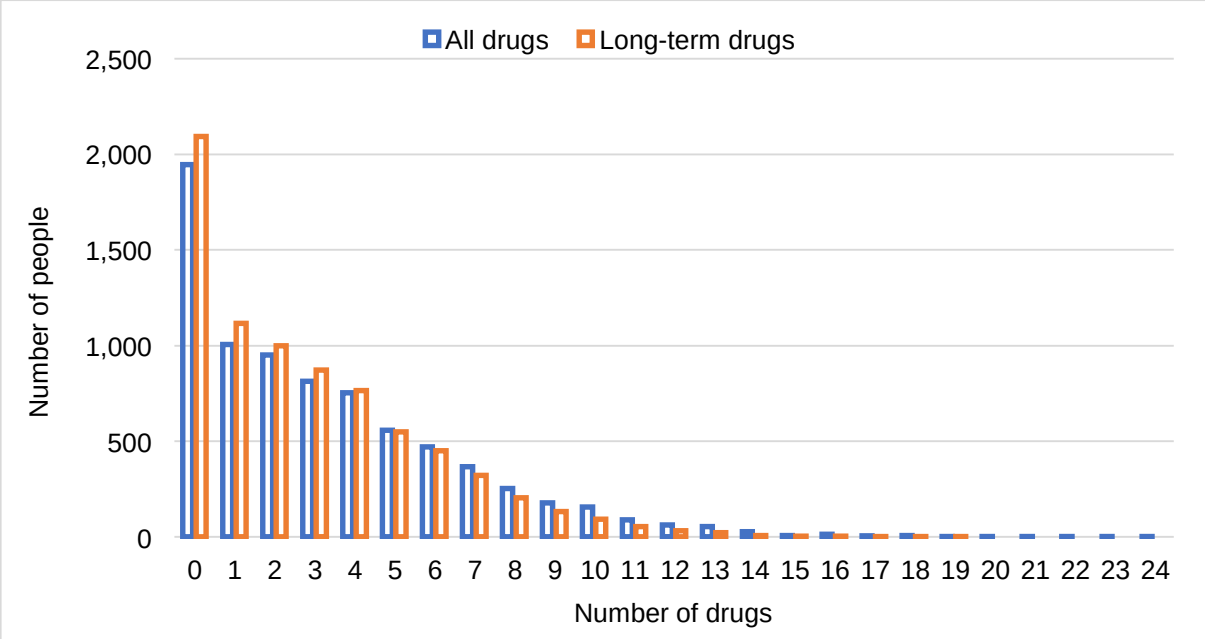
Not including diabetes.

* SD = standard deviation; IQR = interquartile range.

4.3.1 Description of medications and the association with diabetes

Before introducing the prevalence of and risk factors for polypharmacy, this subsection summarises the information on medications and comorbidities in ELSA 2012. The maximum number of concurrent medications was 24 in one participant, but this dropped to 19 when exclusively long-term medications were counted, as shown in Figure 4.2. The positive correlation between long-term medications and conditions was also confirmed, with a correlation coefficient of 0.74.

Figure 4.2 Number of drugs and long-term drugs, ELSA 2012



I further examined whether the numbers of long-term medications and conditions differed by diabetes status. People with diabetes showed significantly higher numbers of medications and conditions than those without diabetes, as shown in Table 4.5. Figures Figure 4.3 and Figure 4.4 also show that people with diabetes had consistently higher proportions of four or more concurrent medications and three or more illnesses, compared with those without diabetes.

Table 4.5 Number of long-term medications and conditions in ELSA 2012, stratified by diabetes

	No diabetes (N = 6629)	Diabetes (N = 1100)	*P*
Number of drugs, median (IQR)	2 (4)	5 (4)	**< 0.001**
Number of conditions, median (IQR)	2 (2)	3 (3)	**< 0.001**

Figure 4.3 Number of long-term medications in ELSA 2012, stratified by diabetes

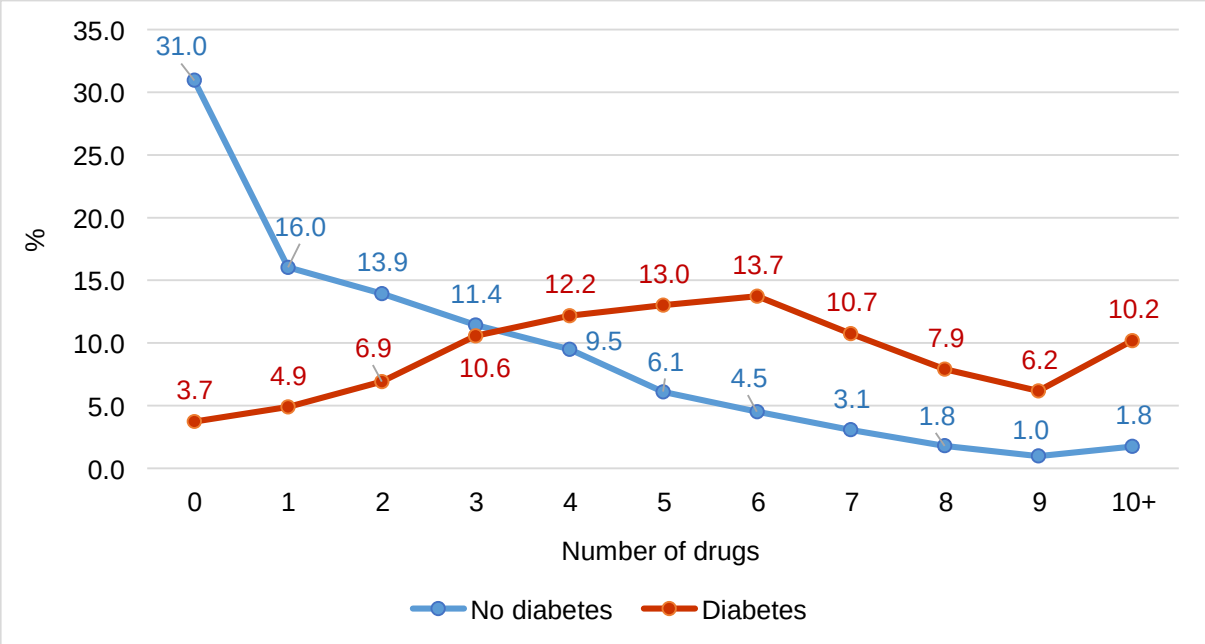
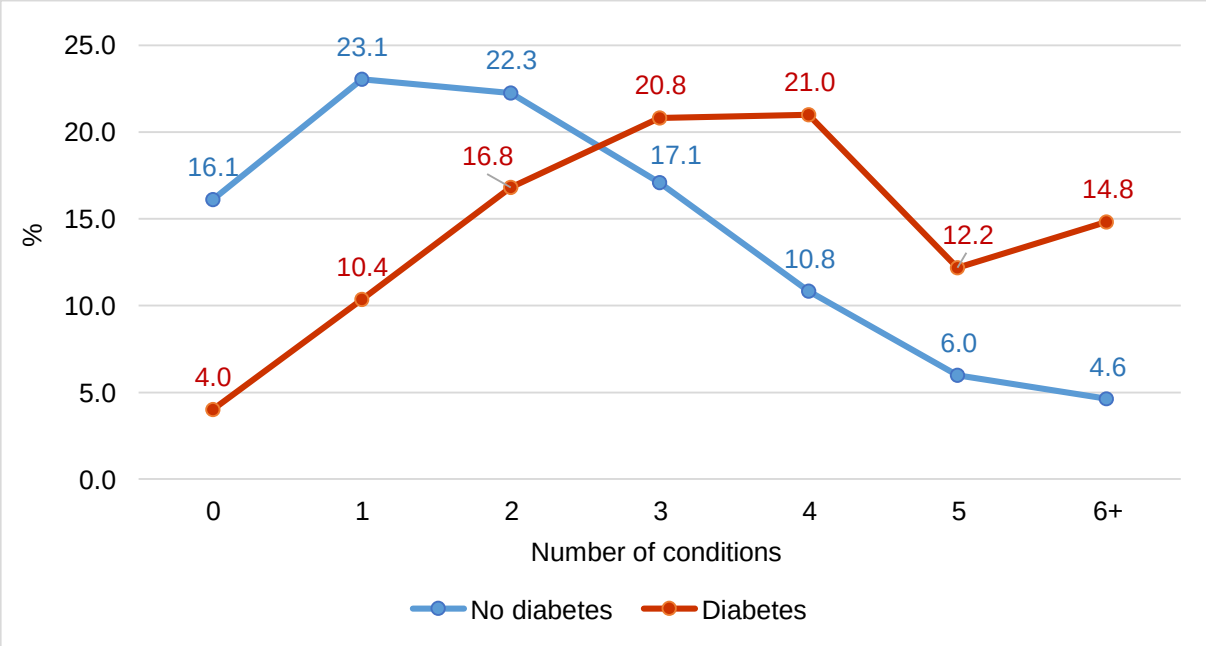


Figure 4.4 Number of long-term conditions in ELSA 2012, stratified by diabetes



The prevalence of long-term medication categories is summarised in Table 4.6; the prevalence of the remaining medications – which presumably were not in long-term use – is displayed in Appendix C-1, except for three medication groups that had fewer than 10 cases (i.e. orlistat for obesity; drugs for febrile convulsion; and pancrelipase, a kind of enzyme). Older people with diabetes showed significantly higher prevalence rates of both long-term and temporary use of most of the medications than those without diabetes. For example, people with and without diabetes showed a great disparity in medicines for CVD (80.8% versus 42.3%), hyperlipidaemia (70.9% versus 28.2%), and peptic ulcers and gastroesophageal reflux disease (31.9% versus 19.6%).

Table 4.6 Prevalence of long-term medications in ELSA 2012, stratified by diabetes

Medication category	No diabetes (N = 6629) N (%)	Diabetes (N = 1100) N (%)	Total (N = 7729) N (%)
Diabetes	–	681 (62.0)	682 (8.8)
Diabetic neuropathy	6 (0.1)	11 (1.0)*	17 (0.2)
CVD	2801 (42.3)	889 (80.8)*	3690 (47.7)
Hyperlipidaemia	1872 (28.2)	779 (70.9)*	2651 (34.3)
Hyperuricemia (including gout)	143 (2.2)	50 (4.6)*	193 (2.5)
Lung disease (including inhalers)	826 (12.5)	175 (15.9)*	1001 (13.0)
Bone disease	242 (3.7)	52 (4.7)	294 (3.8)
Psychiatric conditions	724 (10.9)	187 (17.0)*	911 (11.8)
Epilepsy (seizure)	151 (2.3)	30 (2.7)	181 (2.3)
Parkinson's disease	60 (0.9)	8 (0.7)	68 (0.9)
Dementia (including Alzheimer's disease)	15 (0.2)	4 (0.4)	19 (0.3)
Inflammatory bowel disease	41 (0.6)	6 (0.6)	47 (0.6)
Autoimmune disease (rheumatic disease, myasthenia gravis)	133 (2.0)	25 (2.3)	158 (2.0)
Cancer	85 (1.3)	23 (2.1)*	108 (1.4)
Hormone therapy	680 (10.3)	134 (12.2)	814 (10.5)
Treatment for substance dependence (including alcohol, opioid, and smoking)	17 (0.3)	0	17 (0.2)
Sedative (hypnotic)	111 (1.7)	23 (2.1)	134 (1.7)
Tremor	14 (0.2)	6 (0.6)*	20 (0.3)
Symptom relief for pain, inflammation and rheumatic disease	433 (6.5)	60 (5.5)	493 (6.4)
Pain relief			
Opioid derivatives	287 (4.3)	93 (8.5)*	380 (4.9)
Trigeminal neuralgia	31 (0.5)	4 (0.4)	35 (0.5)
Migraine (including headache)	81 (1.2)	9 (0.8)	90 (1.2)
Peptic ulcers and gastroesophageal reflux disease	1298 (19.6)	351 (31.9)*	1649 (21.3)
Supplements for people with bone disease	274 (4.1)	53 (4.8)	327 (4.2)
Others†	642 (9.7)	171 (15.6)*	813 (10.5)

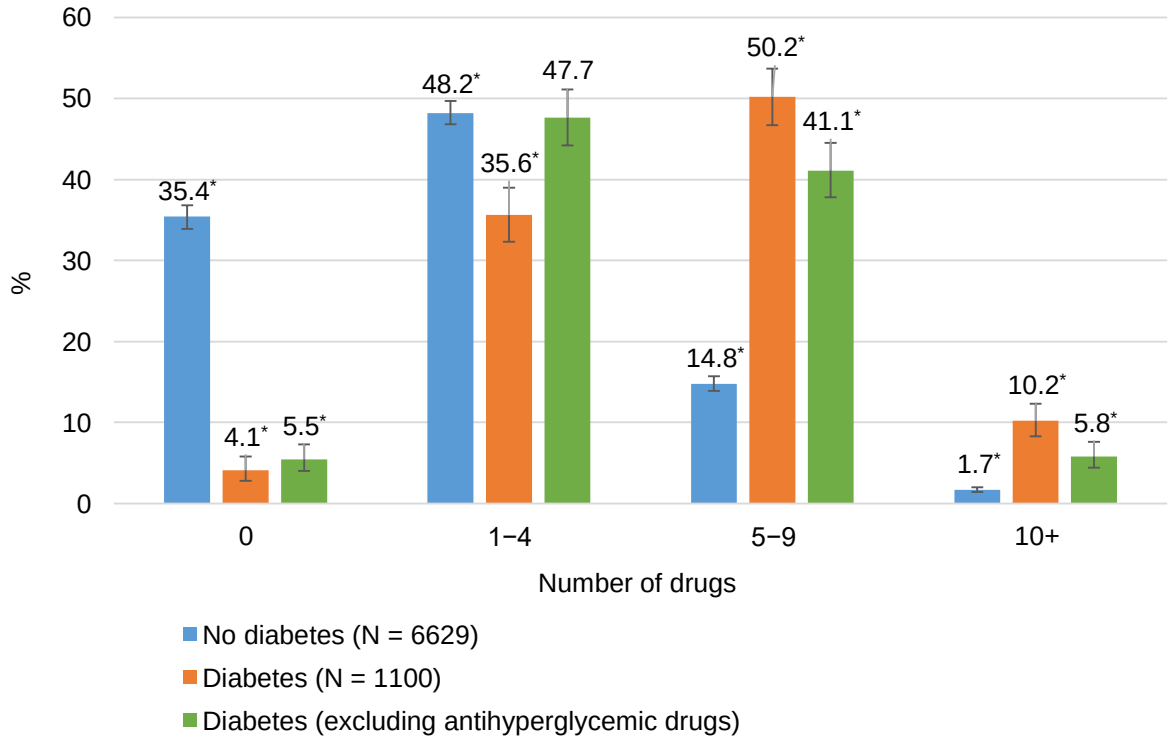
* Significantly higher proportions in people with diabetes.

† Others included drugs for attention deficit hyperactivity disorder, Tourette's syndrome, benign prostatic hyperplasia, urinary incontinence, urine alkalinisation, ureteric colic, thyrotoxicosis, nocturnal cramps, dry mouth, and sputum viscosity.

4.3.2 Prevalence of polypharmacy and heightened polypharmacy

Among 7729 participants, 2093 (31.1%) did not take any drugs, 3752 (46.5%) took one to four long-term medications a day, 1656 (19.6%) took five to nine medications (polypharmacy), and 228 (2.8%) took 10 or more medications (heightened polypharmacy). As Figure 4.5 shows, significant differences in the prevalence rates emerged when the study samples were divided by diabetes status. Among people with diabetes, only 4.1% did not take long-term medications, while 35.4% of people without diabetes did not. People with diabetes tended to take more medications, with a higher prevalence of polypharmacy (50.2% versus 14.8%) and heightened polypharmacy (10.2% versus 1.7%) than those without diabetes ($P < 0.001$). The gap in the prevalence between the two groups remained significant even when antihyperglycemic drugs were excluded: for people with diabetes, the prevalence of polypharmacy dropped from 50.2% to 41.1%, and heightened polypharmacy dropped from 10.2% to 5.8% (Figure 4.5). Detailed information on sample sizes, prevalence rates, and 95% CIs for the four categories, both including and excluding antihyperglycemic agents, is additionally summarised in Appendix C-2.

Figure 4.5 Prevalence of polypharmacy in ELSA 2012, stratified by diabetes



* Significantly different between people with and without diabetes ($P < 0.001$). Polypharmacy was defined as five to nine drugs; heightened polypharmacy was defined as 10+ drugs.

4.3.3 Risk factors for polypharmacy and heightened polypharmacy

The associations between potential risk factors and polypharmacy and heightened polypharmacy in people without diabetes are summarised in Table 4.7. Factors significantly associated with a higher risk of polypharmacy were older age (RRR = 1.04 per each year increase in age, 95% CI = 1.03, 1.05), living with a partner (RRR = 1.40, 95% CI = 1.12, 1.75), having a higher number of conditions (RRR = 2.43, 95% CI = 2.27, 2.60), being a current smoker (RRR = 1.76, 95% CI = 1.28, 2.42), obesity (high BMI and waist circumference) (RRR = 1.70, 95% CI = 1.37, 2.12), and reporting a higher number of depressive symptoms (RRR = 1.07, 95% CI = 1.02, 1.13). Females (RRR = 0.74, 95% CI = 0.61, 0.90), those in the richest wealth group (RRR = 0.64, 95% CI = 0.45, 0.90), and those with better cognitive function (RRR = 0.95, 95% CI =

0.93, 0.98) were less likely to show polypharmacy. Better cognitive function (RRR = 0.90, 95% CI = 0.83, 0.97) was related to a lower risk of heightened polypharmacy, whereas a larger number of long-term conditions (RRR = 3.81, 95% CI = 3.23, 4.49) and a higher number of depressive symptoms (RRR = 1.14, 95% CI = 1.01, 1.29) were associated with increased risk. Other factors assessed in the study were not significantly related to heightened polypharmacy.

Table 4.8 shows the risk factors for polypharmacy and heightened polypharmacy among people with diabetes. After all other factors were accounted for, females were less likely to show polypharmacy (RRR = 0.51, 95% CI = 0.35, 0.73) and heightened polypharmacy (RRR = 0.51, 95% CI = 0.25, 1.01) than males. Having a larger number of long-term conditions (RRR = 1.86, 95% CI = 1.63, 2.13; RRR = 3.51, 95% CI = 2.77, 4.45) and being obese with high BMI and waist circumference (RRR = 1.68, 95% CI = 1.10, 2.57; RRR = 3.68, 95% CI = 1.31, 10.35) significantly increased the risk of polypharmacy and heightened polypharmacy respectively. A higher number of depressive symptoms (RRR = 1.24, 95% CI = 1.06, 1.46) was related to heightened polypharmacy only.

Table 4.7 Risk factors for polypharmacy in people without diabetes (N = 5372), ELSA 2012

	Polypharmacy (N = 806)			Heightened polypharmacy (N = 72)		
	RRR*	95% CI	*P*	RRR*	95% CI	*P*
Age	1.04	1.03, 1.05	**< 0.001**	1.02	0.98, 1.05	0.358
Female gender	0.74	0.61, 0.90	**0.002**	0.66	0.38, 1.16	0.147
Non-white ethnicity	0.75	0.36, 1.60	0.46	2.41	0.59, 9.87	0.221
Total wealth						
2nd	0.89	0.67, 1.18	0.413	1.24	0.60, 2.56	0.554
3rd	0.78	0.58, 1.05	0.099	0.87	0.40, 1.91	0.727
4th	0.98	0.72, 1.33	0.874	1.12	0.46, 2.68	0.806
5th quintile (richest)	0.64	0.45, 0.90	**0.01**	0.84	0.32, 2.21	0.724
No educational qualifications	1.09	0.87, 1.36	0.455	1.00	0.55, 1.81	0.996
Manual social class	0.99	0.81, 1.22	0.95	0.88	0.50, 1.56	0.665
Living with a partner	1.40	1.12, 1.75	**0.003**	1.02	0.58, 1.82	0.934
Number of conditions#	2.43	2.27, 2.60	**< 0.001**	3.81	3.23, 4.49	**< 0.001**
Current smoker	1.76	1.28, 2.42	**0.001**	1.89	0.82, 4.36	0.137
Alcohol consumption: daily (5−7 days per week)	1.14	0.91, 1.42	0.265	0.85	0.43, 1.69	0.642
Obesity§						
High BMI and waist circumference	1.70	1.37, 2.12	**< 0.001**	1.14	0.61, 2.13	0.679
Either high BMI or high waist circumference	1.16	0.92, 1.46	0.201	1.08	0.58, 2.02	0.81
Cognitive function	0.95	0.93, 0.98	**0.003**	0.90	0.83, 0.97	**0.008**
Number of depressive symptoms	1.07	1.02, 1.13	**0.006**	1.14	1.01, 1.29	**0.028**

* Unweighted RRR.

Not including diabetes.

§ Normal BMI and waist circumference as the reference group.

Table 4.8 Risk factors for polypharmacy in people with diabetes (N = 783), ELSA 2012

	Polypharmacy (N = 397)			Heightened polypharmacy (N = 66)		
	RRR*	95% CI	*P*	RRR*	95% CI	*P*
Age	1.00	0.98, 1.03	0.707	0.98	0.94, 1.02	0.363
Female gender	0.51	0.35, 0.73	**< 0.001**	0.51	0.25, 1.01	**0.052**†
Non-white ethnicity	1.02	0.47, 2.22	0.963	1.12	0.26, 4.94	0.877
Total wealth						
2nd	0.95	0.57, 1.57	0.831	1.49	0.59, 3.80	0.399
3rd	0.74	0.44, 1.24	0.256	1.95	0.75, 5.06	0.171
4th	1.21	0.68, 2.16	0.521	1.11	0.31, 4.00	0.868
5th quintile (richest)	0.56	0.30, 1.04	0.068	1.21	0.35, 4.21	0.769
No educational qualifications	1.08	0.71, 1.64	0.723	1.04	0.48, 2.22	0.928
Manual social class	1.38	0.95, 2.02	0.091	1.57	0.77, 3.20	0.211
Living with a partner	0.96	0.65, 1.41	0.83	0.98	0.48, 2.01	0.966
Number of conditions#	1.86	1.63, 2.13	**< 0.001**	3.51	2.77, 4.45	**< 0.001**
Current smoker	1.30	0.74, 2.29	0.359	1.26	0.45, 3.54	0.662
Alcohol consumption: daily (5−7 days per week)	0.96	0.59, 1.54	0.852	0.53	0.18, 1.55	0.245
Obesity§						
High BMI and waist circumference	1.68	1.10, 2.57	**0.016**	3.68	1.31, 10.35	**0.013**
Either high BMI or high waist circumference	1.14	0.71, 1.83	0.574	1.96	0.62, 6.19	0.253
Cognitive function	1.00	0.95, 1.06	0.975	0.97	0.88, 1.07	0.523
Number of depressive symptoms	1.08	0.97, 1.20	0.159	1.24	1.06, 1.46	**0.009**

* Unweighted RRR.

Not including diabetes.

† Borderline significant.

§ Normal BMI and waist circumference as the reference group.

Sensitivity analysis

A sensitivity analysis using specific conditions – CVD, hypertension, hyperlipidaemia, and psychiatric conditions – and an illness count of the remaining conditions was carried out. The remaining conditions included 10 diagnoses: lung disease and asthma, arthritis, bone disease, cancer and malignant blood disorder, Parkinson's disease, dementia (including Alzheimer's disease), any one of four eye diseases, hyperuricemia, epilepsy, and inflammatory bowel disease. A larger number of CVDs and remaining conditions and the presence of hypertension, hyperlipidaemia, and psychiatric conditions were associated with an increased likelihood of developing polypharmacy and heightened polypharmacy. Similar estimates for other factors can be observed in Appendices Appendix C-3 and Appendix C-4, demonstrating the robustness of the results. The contribution of different factors to the final results was also examined. The number of long-term conditions was the main contributor to the lack of association between socio-demographic characteristics and polypharmacy, as well as to the attenuation of associations between health factors and polypharmacy. Age effects disappeared when long-term conditions and health factors were adjusted for simultaneously. In addition, diabetes status interacted with age ($p = 0.001$ for polypharmacy, $p = 0.036$ for heightened polypharmacy) and the number of long-term conditions ($p < 0.001$ for polypharmacy, $p = 0.546$ for heightened polypharmacy), justifying the stratification by diabetes in this study. It was found that the interaction between diabetes and age groups (50–59, 60–69, 70–79, 80+) was significant for polypharmacy only ($p < 0.01$). For people without diabetes, the risk of polypharmacy increased with age, while the risk in people with diabetes was similar across age groups. Lastly, the number of antihyperglycemic medications in each age group was

further examined, and people aged 80 and older were found to be taking fewer antihyperglycemic drugs compared with younger age groups.

4.4 Discussion

4.4.1 Summary

A higher prevalence of polypharmacy and heightened polypharmacy was observed among people with diabetes compared with those without diabetes. Risk factors for polypharmacy also differed to some extent according to diabetes status. Among people with diabetes, 50.2% and 10.2% showed polypharmacy and heightened polypharmacy respectively, in contrast to 14.8% and 1.7% in people without diabetes. When antihyperglycemic drugs were excluded, people with diabetes still showed a substantially higher prevalence of polypharmacy (41.1%) and heightened polypharmacy (5.8%) than non-diabetic participants. These results indicate that the elevated rate of polypharmacy among people with diabetes is not merely due to prescriptions for antihyperglycemic medications, and they imply that people with diabetes aged 50 and older tend to have more comorbidities that need pharmacological treatment.

A greater number of long-term conditions was a risk factor for polypharmacy regardless of diabetes status, while other factors were differentially related to polypharmacy in people with and without diabetes. Male gender and obesity were related to polypharmacy and heightened polypharmacy among participants with diabetes, while these relationships were less consistent in those without diabetes. By contrast, a higher number of depressive symptoms and worse cognitive function were consistently associated with polypharmacy and heightened polypharmacy in

participants without diabetes, but not in those with diabetes. On the other hand, several factors were related to polypharmacy (but not heightened polypharmacy) in people without diabetes, including socio-demographic factors (age, gender, the richest quintile of wealth, and cohabitation) and health factors (smoking status and obesity).

The impact of long-term conditions on polypharmacy is well known; however, this was the first study to demonstrate that the association with the number of long-term conditions was similar in people with and without diabetes. The addition of a single long-term condition doubled the risk of polypharmacy and increased the risk of heightened polypharmacy by more than three times. Furthermore, age was not a risk factor for either polypharmacy or heightened polypharmacy among people with diabetes, in contrast with much of the literature (Veehof et al. 2000; Yong et al. 2012; Papazafiropoulou et al. 2014; Lim et al. 2017; Slater et al. 2018; Vicinanza et al. 2018). This suggests that for people with diabetes, health status − long-term conditions and health factors − plays a more prominent role than socio-demographics such as age. Therefore, the findings of this study provide evidence about the characteristics related to a higher risk of polypharmacy among older adults with diabetes.

4.4.2 Comparison with existing literature

Prevalence of polypharmacy

As noted earlier, the prevalence of polypharmacy in the literature varies substantially according to different definitions and study characteristics. In this nationally representative sample, 19.6% of participants had polypharmacy, a prevalence similar to that found in two previous UK-based studies (Rawle et al. 2018; Slater et al. 2018). However, heightened polypharmacy (2.8%) in this study was slightly lower than was

found in those previous studies, where it was 6.4% (Slater et al. 2018) and 4.7% (Rawle et al. 2018). Slater et al. did not limit the definition to long-term or regularly used medications, while Rawle et al. used nine or more medications as the definition of extreme polypharmacy. These differences may account for the differences in the results.

Among participants with diabetes, 50.2% showed polypharmacy, which was similar to the 57.1% reported in the Italian diabetic population aged 65 and older (Noale et al. 2016). The present study was the first to show the gap in prevalence rates between people with and without diabetes, indicating the clinical importance of diabetes in terms of the coexistence of comorbidities and concurrent use of multiple medications.

Risk factors

Diabetes and its complications are well-established risk factors for polypharmacy (Veehof et al. 2000; Kim et al. 2014; Dwyer et al. 2016; Noale et al. 2016; Abolhassani et al. 2017; Lim et al. 2017; Vicinanza et al. 2018); however, this was the first study to evaluate the risk factors for polypharmacy among older people with diabetes separately from those without diabetes. Direct comparisons with previous studies are difficult to make. Slater et al. (Slater et al. 2018) also analysed polypharmacy in ELSA, and identified different risk factors. This may be a result of the different definitions used for long-term conditions and polypharmacy. Slater et al. employed a dichotomous self-reported long-term health condition variable, whereas this study employed a continuous variable indicating the number of long-term conditions, which were self-reported and verified by medication profiles. Also, only long-term medications were

included in the present study's definition of polypharmacy, while Slater and colleagues did not place any restrictions on types of medication.

Despite variations in definitions, there is a consensus that a larger number of long-term conditions increases the risk of the development of polypharmacy and heightened polypharmacy (Yong et al. 2012; Kim et al. 2014; Silveira, Dalastra, and Pagotto 2014; Noale et al. 2016; Lim et al. 2017; Komiya et al. 2018; Ong et al. 2018; Rawle et al. 2018; Tefera, Alemayehu, and Mekonnen 2020). However, other factors vary across diabetes-focused studies. For example, an Italian cross-sectional study of adults aged 65 and older (Noale et al. 2016) reported that females had a 56% increase in the risk of polypharmacy, whereas this study found that women had lower rates of polypharmacy and heightened polypharmacy than men. The same Italian study (Noale et al. 2016) also reported better cognitive performance as a risk factor for polypharmacy, but no relation was found in the diabetic group in this study. Although diabetes is believed to contribute to cognitive impairment (Saedi et al. 2016; Zilliox et al. 2016), the association between cognitive function and polypharmacy remains questionable and may be bidirectional. On the other hand, the estimate of obesity in this study was partially in line with the Italian study (Noale et al. 2016), where BMI 30 or more was a risk factor. Older adults with high values of BMI and waist circumference combined tended to have polypharmacy and heightened polypharmacy, but this association did not exist for those who had only a high BMI or a high waist circumference.

These findings partially support the concept that ageing is related to the development of polypharmacy (Veehof et al. 2000; Yong et al. 2012; Kim et al. 2014; Papazafiropoulou et al. 2014; Abolhassani et al. 2017; Lim et al. 2017; Slater et al. 2018; Vicinanza et al. 2018; Tefera, Alemayehu, and Mekonnen 2020), but the

association seemed stronger among individuals without diabetes. Some characteristics of diabetes, such as diabetic complications and treatment guidelines, may contribute to polypharmacy at an early age. Also, fewer antihyperglycemic drugs were observed in the oldest age group (80 and older). These factors may account for the disappearing association with age among older adults with diabetes.

People without diabetes who had more depressive symptoms and worse cognitive function showed a higher risk of polypharmacy and heightened polypharmacy. Both depression and cognitive impairment are thought to be related to diabetes (Li et al. 2016; Olvera et al. 2016; Saedi et al. 2016; Zilliox et al. 2016), so their association with polypharmacy in people with diabetes may not have appeared in this cross-sectional study.

4.4.3 Strengths and limitations

This study had several strengths. First, the self-reported diagnoses were verified by medication profiles collected by nurses. The verification and collection process helped to reduce misreporting bias. Second, the inclusion of undiagnosed cases decreased misclassification bias. Third, a rigorous definition of polypharmacy was employed that referred to drugs in long-term use, rather than to those in temporary use such as painkillers. Fourth, OTC drugs for long-term conditions were included, since some interactions between OTC and prescribed medications can be life-threatening, such as ACEIs in combination with potassium supplements. Lastly, this study contained comprehensive assessments of multiple factors related to socio-demographic characteristics and health status. ELSA provided the opportunity to investigate associations between these factors and polypharmacy, since previous hospital-based studies have typically not included much information on socio-demographics.

Some limitations of this study should also be acknowledged. Information on drug duration, dose, and frequency was not collected during the nurse visits, so no definite cut-off could be used to define long-term medications, nor could appropriate or problematic polypharmacy be assessed. Despite this limitation, the strong association between diabetes and polypharmacy disclosed in this study can be justified by the burden of comorbidities in people with diabetes regardless of polypharmacy status (Appendix C-5). Also, some combination drugs shared the same code with a single drug that was indistinguishable, so the prevalence of polypharmacy and heightened polypharmacy was underestimated in such cases. Furthermore, a few events of heightened polypharmacy in both the diabetes and non-diabetes groups might have weakened the statistical power to assess multiple risk factors. Finally, this was a cross-sectional study, so causal conclusions could not be drawn, and there may have been underlying unmeasured factors that were responsible for the associations observed.

4.5 Conclusion

Adults with diabetes had a significantly higher prevalence of polypharmacy and heightened polypharmacy than those without diabetes, regardless of whether antihyperglycemic drugs were included. The risk factors for polypharmacy and heightened polypharmacy in the two groups also differed. People with diabetes who were men and obese were more likely to show polypharmacy and heightened polypharmacy. Greater attention to polypharmacy among older people with diabetes would benefit clinical practice, help to detect inappropriate polypharmacy, and potentially help to reduce polypharmacy-associated adverse effects.

Chapter 5. Polypharmacy and mortality

Abstract

Background

Although medicines are prescribed based on clinical guidelines and expected to benefit patients, both positive and negative health outcomes have been reported associated with polypharmacy. Mortality is the main outcome, and information on cause-specific mortality is scarce. Hence, we investigated the association between different levels of polypharmacy and all-cause and cause-specific mortality among older adults.

Methods

The ELSA is a nationally representative study of people aged 50+. From 2012/2013, 6295 individuals were followed up to April 2018 for all-cause and cause-specific mortality. Polypharmacy was defined as taking 5–9 long-term medications daily and heightened polypharmacy as 10+ medications. Cox proportional hazards regression and competing-risks regression were used to examine associations between polypharmacy and all-cause and cause-specific mortality, respectively.

Results

Over a 6-year follow-up period, both polypharmacy (19.3%) and heightened polypharmacy (2.4%) were related to all-cause mortality, with hazard ratios of 1.51 (95% CI 1.05–2.16) and 2.29 (95% CI 1.40–3.75) respectively, compared with no medications, independently of demographic factors, serious illnesses and long-term conditions, cognitive function and depression. Polypharmacy and heightened polypharmacy also showed 2.45 (95% CI 1.13–5.29) and 3.67 (95% CI 1.43–9.46)

times higher risk of CVD deaths, respectively. Cancer mortality was only related to heightened polypharmacy.

Conclusion

Structured medication reviews are currently advised for heightened polypharmacy, but our results suggest that greater attention to polypharmacy in general for older people may reduce adverse effects and improve older adults' health.

This work was published in the *Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* (Huang et al. 2021a).

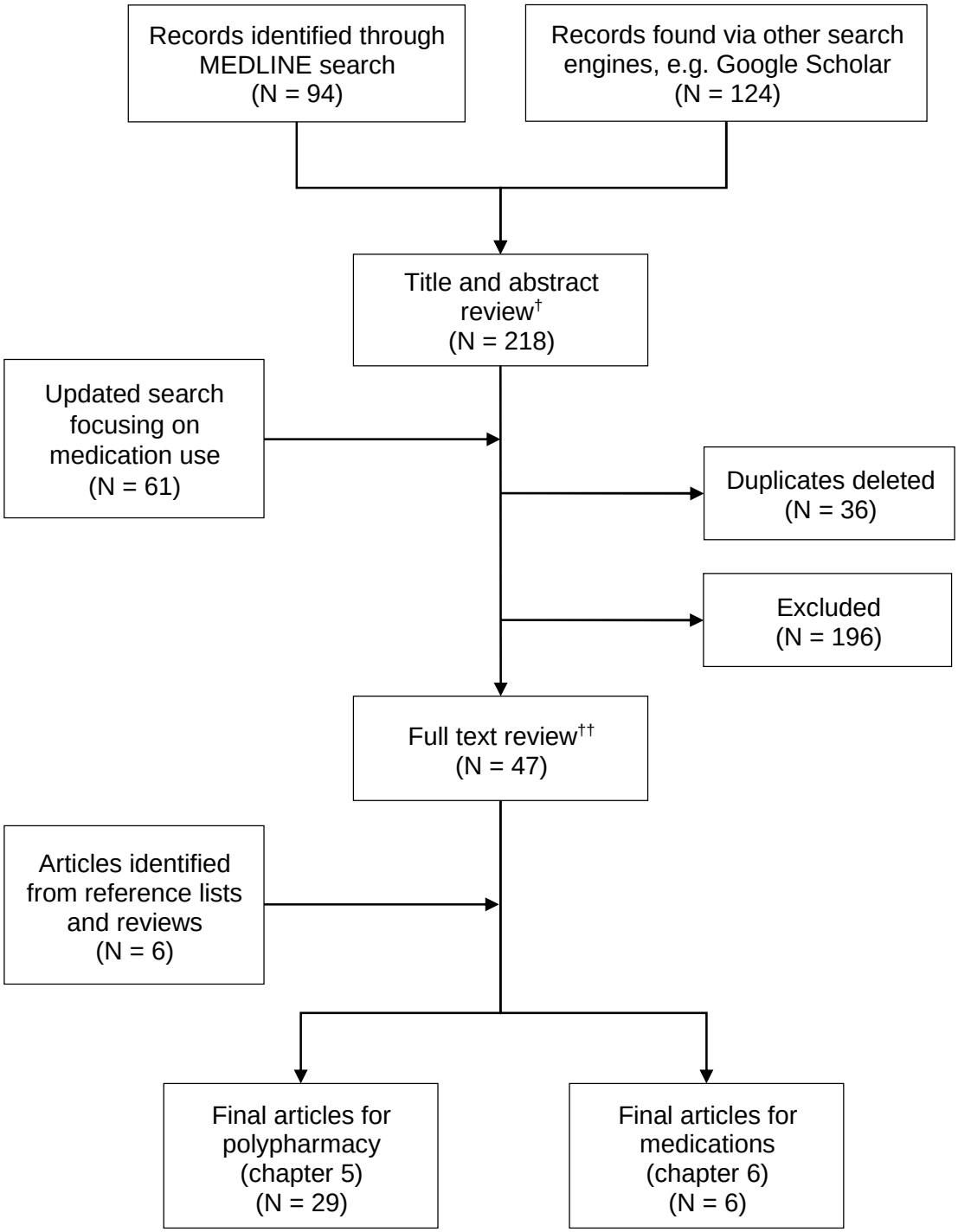
5.1 Background

Medicines are prescribed based on clinical guidelines, and they are expected to benefit patients; however, negative health outcomes have been found to be associated with polypharmacy (Fried et al. 2014; Yashkin et al. 2018). Several adverse health outcomes − falls, adverse drug events, functional decline, cognitive impairment, hospitalisation, and mortality − have been studied widely in community-dwelling older adults (Fried et al. 2014). The different definitions of polypharmacy adopted in different studies make it difficult to draw comparisons, and this has led to a debate about the effects of polypharmacy among older people. In order to understand the existing evidence, a literature search was carried out through the MEDLINE database and Google Scholar using the search terms ‘polypharmacy’, ‘mortality’, and ‘aged’. The search term ‘medication or drug combination’ was additionally employed specifically for articles about medication use and mortality. Studies on the association between polypharmacy and mortality in older people were included for the work discussed in

this chapter, and articles on the relationship between medication use and mortality were selected for subsequent analysis in the work discussed in chapter 6. The literature review process is summarised in Figure 5.1.

The literature on polypharmacy and mortality focuses on all-cause mortality, and information on cause-specific mortality is scarce. Most previous findings from population-based observational studies have shown a positive correlation between polypharmacy and all-cause mortality, independently of pre-existing health conditions (Espino et al. 2006; Richardson et al. 2011; Bowling et al. 2013; Shah et al. 2013; Gómez et al. 2015; Martinez-Gomez et al. 2018; Romano-Lieber et al. 2019). All of these studies took account of specific long-term conditions (e.g. CVDs and diabetes), with an additional adjustment for the total number of long-term conditions in a Brazilian study (Romano-Lieber et al. 2019). Nevertheless, there have been a few studies that do not agree with the association between polypharmacy and all-cause mortality (Lu et al. 2015; Schottker et al. 2017; Yashkin et al. 2018). Many studies that have employed small or specific samples, such as older patients with acute venous thromboembolism or on acute geriatric wards (Alarcon et al. 1999; Jaspers Focks et al. 2016; Schlesinger et al. 2016; Faller et al. 2017; Nightingale, Skonecki, and Boparai 2017; Pelavski et al. 2017), have also supported the role of polypharmacy as an independent predictor of all-cause mortality. In addition, two studies employed comorbidity-polypharmacy scores − the sum of the number of medicines and all known comorbidities − to investigate the relationship with death rates (Evans et al. 2012; Justiniano et al. 2015). However, this new score seemed not to perform well, probably because it did not add more information to the original assessment of polypharmacy and comorbidities.

Figure 5.1 Flow chart of literature review process for polypharmacy/medications and mortality



† Criteria were irrelevance to polypharmacy, very small sample size, case study/report, and pharmaceutical publications about specific medications.

†† Criteria were accessibility of full text in English and exploration of the association between polypharmacy/medications and mortality.

An American study (Yashkin et al. 2018) found that the use of intensive drug therapy delayed death, but not severe macrovascular outcomes, in people aged 65 and older who had been diagnosed with type 2 diabetes and hypertension. Intensive drug therapy was defined as taking five or more distinct medication categories from antihyperglycemic and antihypertensive medicines. Although in line with the cut-off for polypharmacy, this definition was limited to particular drugs, thus making comparisons very difficult. A German study (Schottker et al. 2017) found that the association between polypharmacy and non-cancer mortality disappeared after additional adjustment for a propensity score for polypharmacy. The propensity score assigned each participant a value for their individual propensity to treatment with polypharmacy. The score was computed from an equation containing 39 variables, including socio-demographics, lifestyles, biomarkers, diseases, and disease severity; the coefficients came from a logistic regression model in which polypharmacy was the dependent variable and the 39 variables were independent variables. Although this research involved comprehensive confounders that may have influenced death rates, the rationale of the propensity scores was questionable, and over-adjustment may have been a concern. For example, age was calculated in the propensity scores and also adjusted for in the survival model.

Lastly, a meta-analysis (Leelakanok et al. 2017) showed that polypharmacy was associated with a higher risk of all-cause mortality, regardless of cut-off values for polypharmacy. Among the studies in this meta-analysis, many had short follow-ups; those with follow-ups of five years or more were based on selective non-representative populations (Leelakanok et al. 2017), making it difficult to generalise the results. To date, there have been no observational studies with representative samples exploring

whether polypharmacy is associated with cause-specific mortality. Therefore, mixed findings have been reported regarding the effect of polypharmacy on all-cause mortality, and little is known about whether polypharmacy is related to specific causes of death.

In clinical practice, there are different policies on medication interventions to tackle polypharmacy issues in different areas. NICE recommends that a structured medication review should be carried out for people with polypharmacy, but it does not specify the definition of polypharmacy (NICE 2020). Current interventions in medication use published by NHS England target people with heightened polypharmacy rather than those with polypharmacy, or else target patients with high numbers of addictive pain management medications (NHS England and NHS Improvement 2019). Compared with these two approaches, the Scottish government has set up extensive polypharmacy guidance that targets people on high-risk medications (defined by 17 case-finding indicators), regardless of the number of drugs taken (Scottish Government Polypharmacy Model of Care Group 2018). Because of these disparities in the guidelines on polypharmacy management, as well as the insufficient evidence of a link between polypharmacy and mortality, the aim of this study was to investigate the association between different levels of polypharmacy and all-cause and cause-specific mortality in a nationally representative sample of community-dwelling older adults in England. It was hypothesised that a gradient relationship existed between different levels of polypharmacy and all-cause and cause-specific mortality among older adults, independently of health status. The role of diabetes in this relationship was also explored.

This study improved on previous work on polypharmacy and mortality in several ways: first, by using medication data collected by health professionals; second, by

adopting a rigorous definition of polypharmacy; third, by studying the issue in a nationally representative sample for which a wide range of health and socio-demographic characteristics (e.g. wealth and cohabitation) were available as well as objective measurements of obesity and cognition; lastly, by adopting an appropriate statistical technique (competing-risks regression) to study cause-specific mortality.

5.2 Methodology

5.2.1 Study population

The data came from ELSA Wave 6 (2012–13), during which a total of 9169 interviews with core members had been conducted. Of these, 7730 participants had been visited by a study nurse who recorded information on all medications. Participants who had been diagnosed with cancer or malignant blood disorders (N = 480), who had died within one year of follow-up (N = 82), and who lacked complete information on all variables (N = 905) were excluded, resulting in an analytical sample of 6295 participants.

The nature of cancer justified the exclusion of cancer patients in terms of survival rates and relevant treatments. People with cancer are likely to have a shorter life expectancy unless the cancer is regarded as cured (in complete remission for five years or more). Moreover, most chemotherapy is intravenous and often done in hospitals so that the medication information cannot be collected during home visits. Chemotherapy generally takes three to six months to complete and may have concerning drug-drug interactions with other medications. In this case, the exclusion of cancer patients would ensure the rationale of this study and avoid the overestimation of the risk of medication patterns on mortality.

5.2.2 Polypharmacy

Polypharmacy was defined as taking five to nine long-term medications daily; taking 10 or more medications was defined as heightened polypharmacy. Long-term medications were either drugs for long-term conditions, such as cardiovascular and antihyperglycemic agents, or drugs for long-term symptoms, such as sedatives for insomnia and opioid derivatives for pain relief. OTC drugs used for long-term conditions were also included in this study – for example, calcium supplements for bone disease. Each distinct pharmacological agent was treated as an individual drug, so distinguishable combination drugs were counted according to the number of active ingredients.

5.2.3 Mortality data

Study participants were linked to the NHS's Central Register, which provides vital status data. The month and year of death were recorded for each deceased participant up to the end of follow-up (April 2018). Data regarding causes of death was provided for broad classifications of disease according to the International Classification of Diseases. These classifications included cancer (codes C00–C97), CVD (codes I00–I99), diseases of the respiratory system (codes J00–J99), and other remaining causes. For participants with no record of an event, the data was censored at the end of May 2018.

5.2.4 Potential confounders

Socio-demographic characteristics

A continuous variable for age was employed. Binary variables were employed for gender (male and female) and cohabiting status (living or not with a partner). Wealth was used as the measure of economic resources, since it is more consistently associated with health outcomes at older ages than income (Demakakos, Marmot, and Steptoe 2012). Wealth was computed from detailed assessments of housing wealth, savings, investments, and possessions net of debt (Taylor et al. 2007; Crawford 2012), and was categorised into quintiles.

Health factors

This study included factors that had been reported in the literature or shown to be significantly related to the outcome in the univariable analysis. Long-term conditions in ELSA Wave 6 were derived from either self-reported diagnoses or specific treatments. The self-reported diagnoses were also verified by medication information where possible. Six long-term conditions − diabetes mellitus, CHD, stroke, lung disease (including asthma), Parkinson's disease, and dementia (including Alzheimer's disease) − were included as individual covariates. The remaining long-term conditions − hypertension, other heart problems, hyperlipidaemia, arthritis, bone disease, psychiatric conditions, eye disease, gout/hyperuricemia, epilepsy, and inflammatory bowel disease – were included in the models as an illness count for adjustment. Functional impairment was defined as self-reported difficulty in either activities of daily living (ADLs) or instrumental activities of daily living (IADLs) (Appendix D-1) (Institute for Fiscal Studies 2014; Torres et al. 2016). Mobility difficulty was defined as having

difficulty in 10 movements of the arms or lower limbs, such as walking 100 yards or picking up a five pence coin from a table (Appendix D-1) (Institute for Fiscal Studies 2014). Obesity was derived from BMI and waist circumference, and was categorised into ‘normal BMI and waist circumference’, ‘high BMI and waist circumference’, and ‘either high BMI or high waist circumference’. The cut-off value for BMI was 30, and the cut-offs for waist circumference were 102 cm in males and 88 cm in females. Smoking status (i.e. whether a current smoker or not) was also investigated. Sleep duration was categorised as a binary: seven to nine hours sleep, versus less than seven hours or over nine hours (Chaput, Dutil, and Sampasa-Kanyinga 2018; Martinez-Gomez et al. 2018). Low physical activity was defined by self-report as not engaging in vigorous/moderate-intensity activities at least once a week (Demakakos et al. 2010; Institute for Fiscal Studies 2014). Cognitive function was assessed by immediate and delayed recall memory tests, and scores ranged from zero to 20 (Huang, Steptoe, and Zaninotto 2021). People who self-reported scores for four or more items from the eight-item version of the CES-D were classified as having significant depressive symptoms (Zivin et al. 2010).

5.2.5 Statistical analysis

The association between polypharmacy and all-cause mortality was assessed by Cox proportional hazards regression (Collett 2015). Cox proportional hazards regression is an approach to determine which combination of potentially explanatory variables affects the form of the hazard function when account is taken of the explanatory variables that are likely to influence survival time. In particular, the effect that the main exposure (i.e. polypharmacy status) had on the hazard of death could be studied (Collett 2015). Hazard ratios (HRs) with corresponding 95% CIs and cumulative

hazard functions were provided. The HR represented the ratio of the hazard of death at any time for an individual taking different numbers of medications (one to four, five to nine, and 10 or more) relative to an individual taking no medications. The cumulative hazard function is the cumulative risk of an event occurring by time t, or is interpreted as the expected number of events that will occur in the interval from the time origin to t (Collett 2015). First, I estimated the age- and sex-adjusted model, and then I assessed the contribution of each set of factors separately. Lastly, the fully adjusted model was presented. The Cox regression parallel assumption was tested before the data analysis, and it held. A linear trend of polypharmacy on the HRs was tested by the likelihood ratio test, which compared the value of −2 log Lˆ for the model that contained polypharmacy treated as a categorical variable with the same value for the model that contained polypharmacy treated as a continuous variable (Collett 2015). The test suggested that the HRs increased linearly across the levels of polypharmacy. Possible interaction terms were tested using likelihood ratio tests.

Competing-risks regression based on Fine and Gray's proportional subhazards model (Fine and Gray 1999) was used to analyse cause-specific mortality, and subdistribution hazard ratios (SHRs) with corresponding 95% CIs and cumulative incidence functions (CIFs) were reported. This method is a useful alternative to the Cox regression in the presence of one or more competing risks, as it takes account of competing events that prevent the event of interest from occurring. For example, participants who die from CVD cannot die from other diseases. Thus, this method allows researchers not to overestimate the risk of the main exposure (Feakins et al. 2018). The SHR refers to the direct effect of each variable on the incidence of different causes of death, in the presence of competing risks of death (Collett 2015). The SHR only provides information on the ordering of CIF curves at different levels of covariates,

and it is not equivalent to HR in the conventional framework (Zhang 2017). The CIF, also refers to as the subdistribution function, is the probability of surviving until t where death is from a specific cause, in the presence of all other risks (Collett 2015). The proportionality of hazards and subhazards was tested by using Schoenfeld residuals (Hess 1995; Zhang 2017), and no violation of assumptions was observed. Multiple imputations were not employed due to the fact that Stata has limited multiple imputation functions incorporating competing risk analysis. Statistical analyses were conducted using Stata (version 15.1; StataCorp LP, College Station, TX, USA).

Sensitivity analysis

Several sensitivity analyses were performed to test the robustness of the main findings. The first sensitivity analysis (SA1) involved adding specific known problematic drug-disease interactions (Table 5.1) (Lindblad et al. 2006; Wooten 2012) in the main model. The second sensitivity analysis (SA2) included alcohol consumption as a covariate. The sample size for this model was smaller (N = 5805) compared with the primary model (N = 6295) due to the variable alcohol being collected in the self-completion questionnaire. The third sensitivity analysis (SA3) additionally adjusted for an indicator of inconsistency between medication use and self-reported conditions in the main model, as some participants took cardiovascular or lipid-lowering medications but did not report relevant diagnoses. Since health status and death are strongly correlated, analyses with different adjustments of health status were carried out. Multimorbidity, defined as the coexistence of two or more long-term conditions, was used instead of long-term conditions (specific conditions and an illness count) in the fourth sensitivity analysis (SA4); all long-term conditions were adjusted

for individually rather than using an illness count in the fifth sensitivity analysis (SA5). Lastly, the sixth sensitivity analysis (SA6) repeated the primary analyses, using one to four medications as the reference instead of no medications.

Table 5.1 List of drug-disease interactions, ELSA 2012

	Drug	Disease
1	Corticosteroids	Diabetes
2	Corticosteroids	Osteoporosis
3	Antipsychotics	Parkinson's disease
4	NSAIDs	Hypertension
5	Anticholinergics/TCAs/BZDs	Dementia

5.3 Results

Of 6295 participants, 1844 (29.3%) did not take long-term medications, 3088 (49.1%) took one to four medications a day, 1214 (19.3%) took five to nine medications (polypharmacy), and 149 (2.4%) took 10 or more medications (heightened polypharmacy). The cohort characteristics are summarised in Table 5.2. People in the polypharmacy and heightened polypharmacy categories tended to be older, be poorer, live without a partner, have more long-term conditions (particularly diabetes, CHD, stroke, lung disease, Parkinson's disease, and dementia (including Alzheimer's disease), along with a higher number of the remaining conditions), report functional impairment and mobility difficulty, be obese, smoke currently, sleep inadequately, report low physical activity, have worse cognitive performance, and have significant depressive symptoms. Taking a greater number of drugs was also related to more all-cause and cause-specific deaths (Table 5.3).

Table 5.2 Baseline characteristics[†] according to number of concurrent drugs, ELSA 2012

	None (N = 1844) % (N)	1−4 drugs (N = 3088) % (N)	5−9 drugs[*] (N = 1214) % (N)	10+ drugs[*] (N = 149) % (N)
Age (years) mean (SD)	62.9 (7.9)	67.8 (8.8)	71.9 (8.7)	71.8 (8.5)
Women	52.9 (975)	57.7 (1783)	54.7 (664)	58.4 (87)
Total wealth				
1 (lowest)	15.1 (279)	18.1 (559)	28.2 (343)	33.6 (50)
2	16.1 (296)	20.2 (625)	23.2 (281)	21.5 (32)
3	19.9 (367)	20.4 (630)	19.4 (236)	22.1 (33)
4	23.3 (429)	20.2 (624)	18.2 (221)	12.1 (18)
5 (highest)	25.6 (473)	21.1 (650)	11.0 (133)	10.7 (16)
Living with a partner	75.2 (1387)	71.3 (2201)	63.3 (768)	56.4 (84)
Diabetes mellitus	1.7 (32)	9.8 (302)	33.2 (403)	49.0 (73)
CHD	0.6 (11)	5.1 (156)	26.8 (325)	48.3 (72)
Stroke	0.3 (6)	3.3 (102)	11.9 (144)	14.8 (22)
Lung disease (including asthma)	3.7 (69)	16.5 (510)	28.4 (345)	53.0 (79)
Parkinson's disease	0.0 (0)	0.8 (25)	1.7 (21)	1.3 (2)
Dementia (including Alzheimer's disease)	0.2 (3)	0.5 (16)	1.9 (23)	2.7 (4)
Number of conditions[#] median (IQR)	1.0 (1.0)	2.0 (2.0)	3.0 (2.0)	4.0 (2.0)
Functional impairment[§]	7.3 (135)	17.0 (524)	38.1 (463)	58.4 (87)
Mobility difficulty[§§]	30.6 (564)	50.9 (1571)	77.8 (944)	94.0 (140)
Obesity				
High BMI and waist circumference	20.0 (368)	28.2 (872)	41.9 (509)	53.0 (79)
Either high BMI or high waist circumference	18.8 (346)	26.1 (806)	26.2 (318)	24.8 (37)
Current smoker	11.9 (219)	8.7 (269)	12.3 (149)	18.1 (27)
Sleep duration < 7 or 9+ hours	36.2 (667)	39.4 (1215)	44.7 (543)	54.4 (81)
Low physical activity	8.8 (162)	17.3 (534)	35.8 (434)	63.1 (94)
Cognitive function mean (SD)	11.9 (3.2)	11.0 (3.4)	9.8 (3.5)	8.7 (3.7)
Depressive symptoms 4+	6.8 (126)	10.0 (309)	17.1 (207)	33.6 (50)

[†] All characteristics showed significantly different proportions among the four groups.

[*] Polypharmacy refers to taking five to nine drugs; heightened polypharmacy refers to taking 10 or more drugs.

[#] The other remaining conditions, not including diabetes mellitus, CHD, lung disease, Parkinson's disease, and dementia (including Alzheimer's disease).

[§] Defined as any difficulty in either ADLs or IADLs.

[§§] Defined as any difficulty with movement of the arms or lower limbs.

Table 5.3 Mortality[†] according to number of concurrent drugs, ELSA 2018

	None (N = 1844) % (N)	1−4 drugs (N = 3088) % (N)	5−9 drugs (N = 1214) % (N)	10+ drugs (N = 149) % (N)
All-cause mortality	3.1 (57)	6.6 (205)	16.1 (196)	27.5 (41)
Cause-specific mortality				
CVD	0.7 (13)	1.7 (51)	6.7 (81)	10.7 (16)
Cancer	1.4 (26)	2.4 (74)	4.0 (48)	8.1 (12)
Respiratory disease	0.4 (7)	0.8 (26)	2.4 (29)	5.4 (8)
Other cause	0.6 (11)	1.8 (54)	3.1 (38)	3.4 (5)

[†] Data was collected before May 2018.

Table 5.4 shows the results of the association between the number of concurrent drugs and all-cause mortality from the Cox proportional hazards regression. Concurrent use of one to four medications was not related to a higher risk of mortality, while polypharmacy (HR = 1.51, 95% CI = 1.05, 2.16) and heightened polypharmacy (HR = 2.29, 95% CI = 1.40, 3.75) showed a higher risk of all-cause mortality compared with not taking medications in the fully adjusted model. The linear trend further supported the dose-response relationship between polypharmacy and all-cause mortality. Statistical adjustment for long-term conditions led to the greatest attenuation of the hazards of polypharmacy (2.10 to 1.49) and heightened polypharmacy (4.22 to 2.51) for all-cause mortality, followed by adjustments for disability (functional impairment and mobility difficulty) and lifestyle factors (obesity, smoking status, sleep duration, and physical activity). The adjustment for diabetes revealed an effect similar to lifestyle factors, albeit slightly weaker. Other factors − wealth and cohabitation, cognitive function, and depressive symptoms – also attenuated the association with polypharmacy, but their impact was relatively small.

In addition to polypharmacy and heightened polypharmacy, factors independently associated with a higher risk of all-cause mortality were older age, having diabetes, CHD, or lung disease, being a current smoker, and reporting low physical activity (Appendix D-2). By contrast, several factors were linked to a lower risk of death, including being female, living with a partner, being obese, and showing better cognitive function.

The role of diabetes in the association between polypharmacy status and all-cause mortality was examined in two different ways, first as a confounder and second as an effect modifier. In the first instance, the diagnosis of diabetes was adjusted separately to observe its effect on the attenuation of the association between polypharmacy and death. The magnitude of the reduction in HRs for polypharmacy and heightened polypharmacy was more than 10% compared with the basic model, indicating that diabetes acted as a confounder. To explore the possibility that diabetes was an effect modifier, interaction terms between diabetes and other covariates were tested, and no significant interactions were identified by likelihood ratio tests. The number of deaths was 499 people out of 6295 participants, which was not large, so there may not have been sufficient statistical power to detect diabetes as an effect modifier. As a result, diabetes was established to be a confounder in the association between polypharmacy and all-cause mortality rather than an effect modifier. The presence of diabetes was also related to a higher risk of all-cause mortality, conditional on the same polypharmacy status.

Table 5.4 Associations between number of concurrent drugs and all-cause mortality in England in 2012−18

	None	1−4 drugs		5−9 drugs*		10+ drugs*		
N = 6295 (499 deaths)	HR	HR* (95% CIs)	*P*	HR* (95% CIs)	*P*	HR* (95% CIs)	*P*	*Trend*††
Age and gender (basic model)	1.00 (Ref)	1.20 (0.89, 1.61)	0.228	2.10 (1.55, 2.84)	**< 0.001**	4.22 (2.82, 6.33)	**< 0.001**	
Basic model + wealth, cohabitation	1.00 (Ref)	1.17 (0.86, 1.57)	0.315	1.98 (1.46, 2.69)	**< 0.001**	3.93 (2.61, 5.91)	**< 0.001**	
Basic model + diabetes	1.00 (Ref)	1.17 (0.87, 1.57)	0.303	1.94 (1.42, 2.65)	**< 0.001**	3.79 (2.50, 5.74)	**< 0.001**	
Basic model + long-term conditions§	1.00 (Ref)	1.05 (0.77, 1.44)	0.753	1.49 (1.04, 2.13)	**0.031**	2.51 (1.54, 4.09)	**< 0.001**	
Basic model + disability#	1.00 (Ref)	1.14 (0.85, 1.54)	0.386	1.85 (1.36, 2.51)	**< 0.001**	3.50 (2.31, 5.30)	**< 0.001**	
Basic model + lifestyle factors†	1.00 (Ref)	1.20 (0.89, 1.62)	0.222	1.95 (1.43, 2.66)	**< 0.001**	3.58 (2.36, 5.45)	**< 0.001**	
Basic model + cognitive function	1.00 (Ref)	1.17 (0.87, 1.58)	0.289	2.02 (1.49, 2.73)	**< 0.001**	3.81 (2.54, 5.72)	**< 0.001**	
Basic model + depressive symptoms	1.00 (Ref)	1.18 (0.88, 1.59)	0.273	2.02 (1.49, 2.73)	**< 0.001**	3.97 (2.64, 5.96)	**< 0.001**	
All covariates (main model)	1.00 (Ref)	1.09 (0.80, 1.48)	0.603	1.51 (1.05, 2.16)	**0.026**	2.29 (1.40, 3.75)	**0.001**	*Linear*

* Polypharmacy refers to taking five to nine drugs; heightened polypharmacy refers to taking 10 or more drugs.

§ Including six long-term conditions (diabetes, CHD, stroke, lung disease (including asthma), Parkinson's disease, and dementia (including Alzheimer's disease)) and an illness count of the remaining conditions.

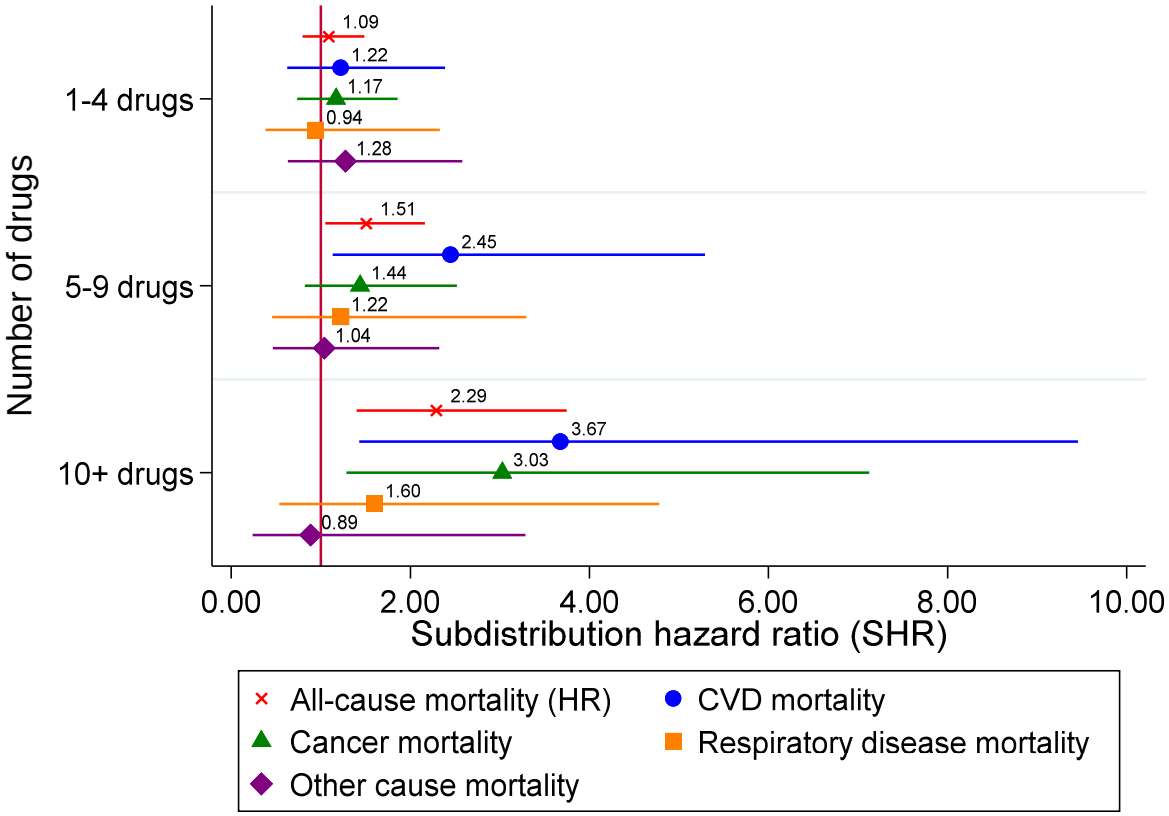
Including functional impairment and mobility difficulty.

† Including obesity and health behaviours (smoking status, sleep duration, and physical activity).

†† A likelihood ratio test was used to test the trend of HRs, and $P > 0.05$ indicated that the trend was linear.

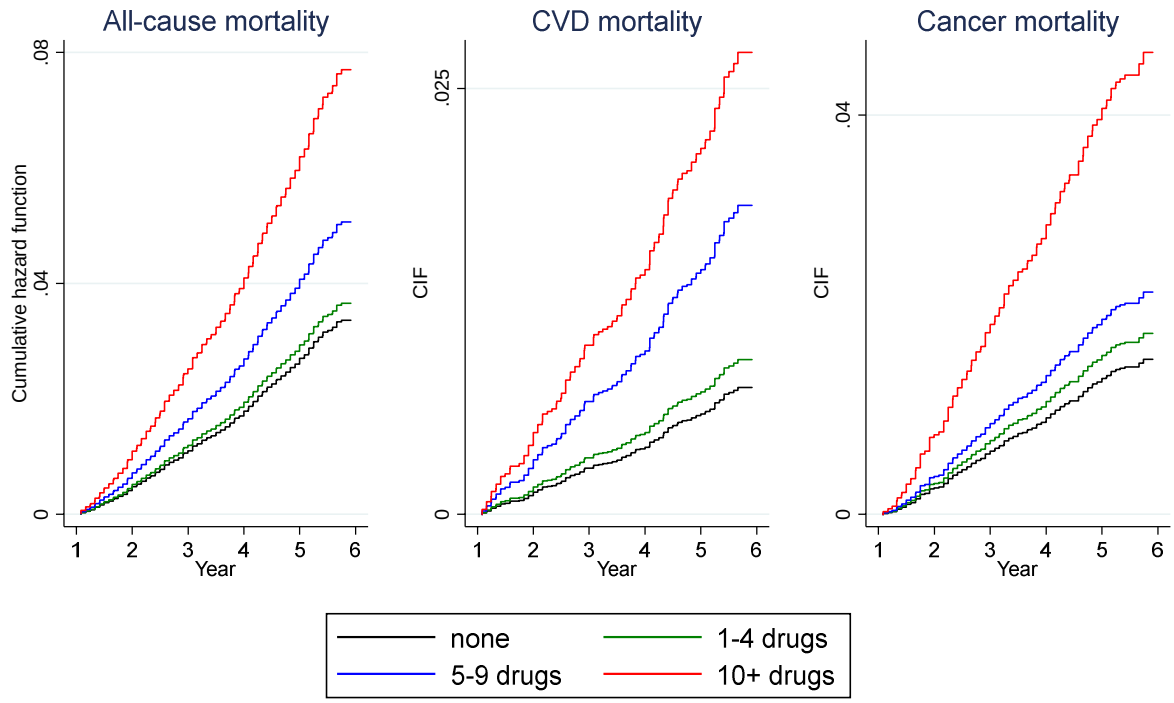
The results for cause-specific mortality obtained from the competing-risks regression are presented in Figure 5.2. Polypharmacy was only related to a higher risk of CVD death (SHR = 2.45, 95% CI = 1.13, 5.29), while heightened polypharmacy was independently associated with CVD mortality (SHR = 3.67, 95% CI = 1.43, 9.46) and cancer mortality (SHR = 3.03, 95% CI = 1.29, 7.13). The 95% CIs of cause-specific mortality were much wider than all-cause mortality due to the smaller sample sizes. The cumulative hazard function of all-cause mortality and the CIF of CVD and cancer mortality are displayed in Figure 5.3. The cumulative hazard function from a Cox proportional hazards regression is the cumulative risk of an event occurring over a time interval, while the CIF from a competing-risks regression denotes estimations of the incidence of the occurrence of an event, taking competing risks into account.

Figure 5.2 Associations[#] between number of concurrent drugs and all-cause and cause-specific mortality in England in 2012−18



[#] Adjusted for age, gender, cohabitation, wealth, six long-term conditions (diabetes, CHD, stroke, lung disease, Parkinson's disease, and dementia), an illness count of the remaining conditions, functional impairment, mobility difficulty, obesity, smoking status, sleep duration, low physical activity, cognitive function, and depressive symptoms.

Figure 5.3 Cumulative hazard function of all-cause mortality and CIF of CVD and cancer mortality for different numbers of concurrent drugs in England in 2012−18



The results of the sensitivity analyses are summarised in Appendix D-3. SA1 took account of known drug-disease interactions (Table 5.1) but showed no important differences from the primary analysis. SA2, which included alcohol consumption, showed a similar dose-response relationship between polypharmacy (HR = 1.57 for polypharmacy, HR = 2.08 for heightened polypharmacy) and all-cause mortality to the primary results (HR = 1.51 for polypharmacy, HR = 2.29 for heightened polypharmacy), although it had a reduced sample size (N = 5805). The variable of alcohol consumption was not included in the primary analysis due to some of its limitations, which might have hampered the results of the study. First, the information on alcohol consumption had been collected by a self-completion questionnaire and had a large number of non-responses. Second, information on the number of days in which the respondent had an alcoholic drink over the previous 12 months was

collected, which is subject to recall bias. Lastly, the frequency of alcohol may not be the best measurement of alcohol consumption (as opposed to the number of units of alcohol). SA3 additionally adjusted for an indicator of inconsistency between medication use and self-reported conditions, because 10.2% of the participants were on particular medications without corresponding diagnoses. The estimates for polypharmacy (HR = 1.60) and heightened polypharmacy (HR = 2.47) were slightly higher than in the primary analysis but remained robust. Furthermore, the adjustment for multimorbidity (defined as two or more long-term conditions) (Geneva: WHO 2016) in SA4 led to an increase in the magnitude of the HRs for polypharmacy (HR = 1.86) and heightened polypharmacy (HR = 3.19) compared with those found in the main analysis (HR = 1.51 for polypharmacy, HR = 2.29 for heightened polypharmacy). However, there was a close relationship between polypharmacy and multimorbidity, where 96.9% and 98.7% of participants in the polypharmacy and heightened polypharmacy groups had multimorbidity compared with 21.5% of people who had multimorbidity in the no-drug treatment group. The presence of multimorbidity appeared not to adjust for long-term conditions properly, so the estimates may have been unreliable. Moreover, SA5 modelled all long-term conditions individually instead of combining some conditions into an illness count, and it obtained similar results to the primary analysis. Finally, SA6 employed one to four medications as the reference group instead of no medications. The findings for all-cause and cause-specific mortality were similar to the primary results, confirming the robustness of this study (Appendix D-4).

5.4 Discussion

5.4.1 Summary

Over a six-year period, polypharmacy and heightened polypharmacy showed a dose-response relationship with all-cause and CVD mortality among older adults in England. In addition, cancer mortality was associated with heightened polypharmacy, even though people who had cancer at baseline were excluded. The presence of long-term conditions, as expected, played the most important role in the association between polypharmacy and all-cause mortality, but this association remained significant and robust even after pre-existing illnesses and demographic and other factors were taken into account.

The robustness of the main findings was largely confirmed by sensitivity analyses, indicating that polypharmacy was an independent risk factor for all-cause, CVD, and cancer mortality among community-dwelling older adults. The results also suggested that multimorbidity appeared to be an inappropriate assessment of the health condition of older adults and tended to overestimate the risk of death posed by polypharmacy, further suggesting that adjustment for specific long-term conditions and the sum of the remaining conditions would be more appropriate.

The underlying mechanism for the association between polypharmacy and mortality could be explained by long-term conditions and the regular use of medications. In the analysis, an adjustment for long-term illness was performed; however, disease severity could not be taken into account, due to the unavailability of this information in ELSA. Disease severity is rarely collected in observational studies, due to the difficulty of recording or measuring this information. Some studies have adopted the Charlson Comorbidity Index; however, this index only considers disease

severity for particular conditions (liver disease, diabetes, and solid tumour) (Sundararajan et al. 2004). Clinically, patients at advanced stages of an illness are likely to take more medications than patients at the initial stage, since combination therapy can increase treatment efficacy. The adjustment of dichotomous long-term conditions only reflects that all patients at different stages are exposed to the condition, but it fails to consider that different stages entail a different severity of the condition. Therefore, the number of medications may to some extent reflect the severity of the disease, resulting in the inference that polypharmacy performs as a predictor of death in older populations.

The association between polypharmacy and death might also be attributed to medications and their potential interactions. Older people may have higher chances of developing problematic polypharmacy because of pharmacokinetic and pharmacodynamic alterations (Delafuente 2008). For example, in older adults some medications become high-risk, and some drug-drug interactions become severe. Although it can be assumed that major drug-drug interactions are avoided by GPs and pharmacists in clinical settings, minor drug-drug interactions may arise or worsen in this population.

5.4.2 Comparison with existing literature

The association between polypharmacy and all-cause mortality observed in this study is supported by previous studies that used survival analysis (Richardson et al. 2011; Bowling et al. 2013; Shah et al. 2013; Martinez-Gomez et al. 2018; Romano-Lieber et al. 2019) as well as one meta-analysis (Leelakanok et al. 2017). The results of this study do not agree with studies that failed to find an association between polypharmacy and mortality based on estimates from logistic regression (Sganga et

al. 2015; Schlesinger et al. 2016; Pelavski et al. 2017). The exception is a Chinese study on men aged 80 and older that showed a positive association using logistic regression (Wang et al. 2015). There are also variations in the literature as to which group is used as the reference category for polypharmacy, ranging from between zero and one medications to fewer than 10 medications (Bowling et al. 2013; Shah et al. 2013; Martinez-Gomez et al. 2018; Romano-Lieber et al. 2019). The findings of this study demonstrated that polypharmacy was related to higher risks of all-cause, CVD, and cancer mortality compared with either taking no medications or taking one to four medications. A systematic review (Leelakanok et al. 2017) reported that the use of one to four medications was associated with death, but this was not found in this research. Many studies included in this review were based on non-representative populations (e.g. patients with heart failure or schizophrenia), had a hospital-based or institutional-based study design, or had a short-term follow-up. These factors may account for the differences compared with this study.

In addition to long-term conditions, lifestyle factors somewhat attenuated the effect of polypharmacy on all-cause mortality, as was observed in a previous study (Martinez-Gomez et al. 2018). For the first time, disability showed the second greatest attenuation of the association.

Role of diabetes

Different long-term conditions have been identified as independent risk factors for all-cause mortality when the Charlson Comorbidity Index is not used to adjust for health status. Differences in study populations, definitions of polypharmacy, lengths of follow-up, and settings (community, care home, or nursing home) may have contributed to

the differences observed across studies (Shah et al. 2013; Pelavski et al. 2017). Diabetes was found to be a confounder in the association between polypharmacy and all-cause mortality in this study. Diabetes, CHD, and lung disease were identified as independent risk factors for death, conditional on the same level of medication use (i.e. polypharmacy). Among these three conditions, the uniqueness of diabetes has been confirmed in previous research. Both diabetes and diabetes in combination with respiratory diseases were found to be linked to higher risks of mortality in a New Zealand study (Teh et al. 2018). Also, the association between diabetes and mortality has been observed in community residents in England and Wales (Shah et al. 2013) and community-based Mexican Americans (Espino et al. 2006). On the other hand, it has been found that people with diabetes are more likely than people without diabetes to develop multimorbidity, including both physical and mental illnesses (Zghebi et al. 2020). To summarise, diabetes shows a strong relationship with high death rates as well as a high probability of multimorbidity, which in turn is likely to lead to polypharmacy. At the same time, comorbidities, polypharmacy, and mortality are connected and mutually influenced. This complicated network may help to make diabetes a crucial condition in explorations of the association between polypharmacy and mortality. Although more evidence is warranted, in the future some long-term conditions such as diabetes may need more attention, in addition to medication use.

5.4.3 Strengths and limitations

This study had several strengths. First, medication profiles were collected by nurses rather than self-reported, and they were used to verify the self-reported diagnoses. This verification and collection process helped to reduce misreporting bias. Second, this study used a rigorous definition of polypharmacy that referred to medications in

long-term use, rather than the temporary use of painkillers. Third, OTC medications for long-term conditions were included, since some interactions between OTC and prescribed medications can be life-threatening, such as ACEIs in combination with potassium supplements (Burnakis and Mioduch 1984). The study employed a nationally representative sample, followed up for six years, for whom comprehensive characteristics were available, from socio-demographic characteristics to health status. A wider range of potential confounders was adjusted for statistically than has been done in previous research, including cognitive function, mobility impairment, lifestyle factors, and depressive symptoms. Also, competing-risks analyses were conducted for different causes of death to provide accurate estimates, accounting for the event of interest and competing events simultaneously. Lastly, the study provided strong evidence of associations between polypharmacy and death, accounting for characteristics not included in previous studies, such as cohabitation and depressive symptoms.

Some limitations of this study should also be acknowledged. Information on medication type but not on duration, dose, and frequency was collected during the nurse visits. Also, some combination medications were indistinguishable from a single medication, so the amount of polypharmacy may have been underestimated in these cases. The assessment was made at a single time point, and medications may have changed over the follow-up period.

5.5 Conclusion

Polypharmacy and heightened polypharmacy showed dose-response relationships with all-cause and CVD mortality among older adults in England over a six-year follow-

up period. Heightened polypharmacy was also related to a higher risk of cancer mortality. In addition to the structured medication reviews currently advised for heightened polypharmacy, the results of this study emphasised that greater attention to polypharmacy in general for older people might be helpful for reducing adverse effects and improving older adults' health.

Chapter 6. Patterns of medication use and mortality

Abstract

Background

Polypharmacy is common among older people and is associated with an increased mortality risk. However, little is known about whether the mortality risk is related to specific medications among older adults with polypharmacy. This study therefore aimed to investigate associations between high-risk medications and all-cause and cause-specific mortality among older adults with polypharmacy.

Methods

This study included 1356 older adults with polypharmacy (5+ long-term medications a day for conditions or symptoms) from Wave 6 (2012/2013) of the ELSA. First, using the agglomerative hierarchical clustering method, participants were grouped according to the use of 14 high-risk medication categories. Next, the relationship between the high-risk medication patterns and all-cause and cause-specific mortality (followed up to April 2018) was examined. All-cause mortality was assessed by Cox proportional hazards model and competing-risks regression was employed for cause-specific mortality.

Results

Five high-risk medication patterns – a RAAS inhibitors cluster, a mental health drugs cluster, a CNS drugs cluster, a RAAS inhibitors and antithrombotics cluster, and an antithrombotics cluster – were identified. The mental health drugs cluster showed increased risks of all-cause (HR = 1.55, 95%CI = 1.05, 2.28) and CVD (SHR = 2.11, 95%CI = 1.10, 4.05) mortality compared with the CNS drugs cluster over six years,

while others showed no differences in mortality. Among these patterns, the mental health drugs cluster showed the highest prevalence of antidepressants (64.1%), benzodiazepines (10.4%), antipsychotics (2.4%), antimanic agents (0.7%), opioids (33.2%) and muscle relaxants (21.5%). The findings suggested that older adults with polypharmacy who took mental health drugs (primarily antidepressants), opioids and muscle relaxants were at higher risk of all-cause and CVD mortality, compared with those who did not take these types of medications.

Conclusions

This study supports the inclusion of opioids in the current guidance on structured medication reviews, but it also suggests that older adults with polypharmacy who take psychotropic medications and muscle relaxants are prone to adverse outcomes and therefore may need more attention. The reinforcement of structured medication reviews would contribute to early intervention in medication use which may consequently reduce medication-related problems and bring clinical benefits to older adults with polypharmacy.

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6.1 Background

Evidence of an association between polypharmacy (including heightened polypharmacy) and all-cause and CVD mortality has been reported in chapter 5. The findings on all-cause mortality were in line with most of the literature (Espino et al. 2006; Richardson et al. 2011; Bowling et al. 2013; Shah et al. 2013; Gómez et al. 2015; Martinez-Gomez et al. 2018; Romano-Lieber et al. 2019). However, little is

known about which medication combinations within polypharmacy further relate to mortality. Since the main focus of this study was medication use within polypharmacy, the search terms for the literature review were very similar to those used for chapter 5, resulting in considerable overlap between the two reviews. The search term ‘medication or drug combination’ was additionally employed to search for articles about medication use and mortality. Studies on the association between medication use and mortality in older people were included. More details have already been introduced in section 5.1 of chapter 5, and the literature review process for both chapters is combined in Figure 5.1.

There has been plenty of research on the effectiveness of specific medications in treating people with particular illnesses, through both randomised controlled trials and observational studies. To take the common CVDs as an example, the use of statins benefits people without established CVD but with cardiovascular risk factors in terms of all-cause mortality and major cardiovascular events (Brugts et al. 2009). However, this study’s focus was the use of high-risk medications within polypharmacy among community-dwelling older adults, rather than specific medications in a specific population. A small number of studies were identified that explored the associations between medication use and all-cause mortality, but they did not involve polypharmacy status, which would have been more relevant to the interest of this study. Four studies defined the anticholinergic burden using various scales and analysed its association with all-cause mortality, but they obtained different results (Ruxton, Woodman, and Mangoni 2015; Sarbacker et al. 2017; Sevilla-Sanchez et al. 2018; Hanlon et al. 2020). Hanlon et al. and Sarbacker et al. found that the use of anticholinergic medications was related to an increased risk of mortality, regardless of which scale of anticholinergic burden was employed, while a meta-analysis only identified the positive

relationship when using the anticholinergic cognitive burden scale but not using other measurements (i.e. the anticholinergic risk scale and anticholinergic components of the Drug Burden Index) (Ruxton, Woodman, and Mangoni 2015). This relationship was also not observed in Sevilla-Sanchez et al.'s research (2018). Another study on older US Army veterans with chronic pain discovered that the use of opioids, antihistamines, and psychotropics was positively correlated with one-year mortality, whereas skeletal muscle relaxants were related to lower risk (Makris et al. 2015). Moreover, another study published in 2001 (Glynn et al. 2001) investigated the associations between the use of 20 common drug classes and one-year mortality among people aged 65−99 years, according to hospitalised status. Several drug classes (e.g. lipid-lowering agents, CCBs, and anxiolytics) were associated with reduced mortality, whereas some medicines showed higher death rates (e.g. loop diuretics, digitalis, and antiarrhythmic agents). Some medications, however, such as ACEIs, showed inconsistent results between hospitalised and non-hospitalised samples. To date, research on medication use among community-dwelling older people with polypharmacy is still lacking. Findings from several studies have failed to reach a consensus on the kinds of medications that might be harmful or beneficial to older adults.

In addition to the medication categories that have been reported to be related to higher or lower mortality, some medications are believed to have a high probability of adverse effects among older adults, such as opioids, BZDs, and antihypertensive drugs (Wooten 2012; Davies and O'Mahony 2015; Makris et al. 2015; Gerlach et al. 2017). The ageing process is normally accompanied by changes in pharmacokinetics (absorption, distribution, metabolism, and elimination) and pharmacodynamics, resulting in a more unpredictable performance of medications in older adults. The high-

risk medications reported in the literature are largely reflected in the polypharmacy guidance published by the Scottish government (Scottish Government Polypharmacy Model of Care Group 2018). In summary, there is broad agreement on the high-risk medications for older adults due to the higher risk of adverse effects. However, no evidence is currently available on medication types in association with mortality, or on medication use within polypharmacy among older people.

There have been different strategies for the management of polypharmacy in clinical practice, advocated by different organisations. The medication review is specifically targeted at polypharmacy in the NICE guidelines (NICE 2020) and at heightened polypharmacy in the NHS England guidelines (NHS England and NHS Improvement 2019). Apart from the concept of polypharmacy, people on high numbers of addictive pain management medications and those on high-risk medications are advised to have a medication review according to NHS England (NHS England and NHS Improvement 2019) and the Scottish government (Scottish Government Polypharmacy Model of Care Group 2018) respectively. Compared with NICE and NHS England, the Scottish government has set up extensive polypharmacy guidance that targets people on high-risk medications, regardless of the number of drugs taken (Scottish Government Polypharmacy Model of Care Group 2018). High-risk medications are defined by 17 case-finding indicators, denoting the use of specific medications is linked to a high risk of specific symptoms or conditions.

To summarise, there has been little research into the types of medication use within polypharmacy in observational studies of nationally representative older adults. Apart from the finding that polypharmacy is an independent risk factor for mortality, little is known about whether high-risk medications (either singly or in combined use) contribute to added risk among older people with polypharmacy. Also, there are

disparities in the inclusion of high-risk medications in different guidelines. Thus, this study aimed to explore the effect of high-risk medications on mortality for people with polypharmacy. The role of diabetes as an effect modifier in this association was also studied.

To conduct this study, high-risk medications were identified from the literature (Wooten 2012; Davies and O'Mahony 2015; Makris et al. 2015; Gerlach et al. 2017) and subsequently classified into 14 medication categories (explained in detail in section 6.2 below). Cluster analysis was employed to classify participants into different clusters based on their use of the 14 medication categories. Four reasons justified the selection of cluster analysis for this study. First, no strong evidence supported a link between specific medications and higher/lower mortality, especially for older people with multimorbidity. Thus, no appropriate classification of medications could be referenced. Second, the number of people with polypharmacy was not large (N = 1356), even though polypharmacy and heightened polypharmacy had been combined. Entering an additional 14 variables of medication groups into the survival model of mortality would have led to low statistical power and therefore weakened the correlations. Third, previous studies had utilised cluster analysis to group symptoms (Song et al. 2010) or group participants according to conditions (Teh et al. 2018) and analysed the association between clusters and death rates. Cluster analysis in combination with multiple correspondence analysis had also been employed to analyse medication patterns in older adults with multimorbidity (Guisado-Clavero et al. 2019). For example, CVDs frequently coexist with hypertension rather than mental disorders, so CVDs have a closer relationship with hypertension than with mental illness. Accordingly, cluster analysis would group CVDs and hypertension in the same cluster. Similarly, the use of particular medications may strongly relate to other

medicines because some common comorbidities usually coexist. Antithrombotics for CVDs, for instance, would have a stronger correlation with antihypertensive drugs than with mental health medications. Hence, the cluster analysis was expected to group participants according to medication use in the same way as conditions. Lastly, the adoption of cluster analysis allowed the researchers to take concurrent medications into account. The concurrent use of medications is prevalent among older adults and becomes complicated for those with polypharmacy, so this needed to be taken into consideration. The aim of this study was to explore the association between high-risk medications and all-cause and cause-specific mortality among older adults with polypharmacy. It was hypothesised that specific high-risk medications (e.g. anticholinergic agents or opioids) might increase the risk of mortality in older adults with polypharmacy.

6.2 Methodology

6.2.1 Study population

In Wave 6, a total of 9169 interviews with core members were conducted. Of these, 7730 participants were visited by a study nurse who recorded information on all medications. After the exclusion of people who had missing information regarding diabetes diagnosis (N = 1), physical activity and functioning (N = 2), and follow-up time (N = 1), who had been diagnosed with cancer or malignant blood disorders (N = 480), and who took hormone therapy that was primarily for cancers (codes 080302 and 080304) (N = 19), 1705 participants with polypharmacy were involved in the cluster analysis. The groups of people with polypharmacy and heightened polypharmacy were combined, referred to here as taking five or more long-term medications per day. After

the cluster analysis was carried out, participants who did not have complete information on variables in the model (N = 328) and those who had died within one year of follow-up (N = 21) were further excluded, resulting in an analytical sample of 1356 individuals with polypharmacy for the survival analysis.

6.2.2 High-risk medications

High-risk medications for older people were identified from the literature (Wooten 2012; Davies and O'Mahony 2015; Makris et al. 2015; Gerlach et al. 2017) on the grounds that they had a high probability of adverse effects in the ageing population. These high-risk medications were classified into 14 medication categories according to their pharmacological mechanisms (Table 6.1), and they were subsequently employed in cluster analysis to group participants into a set of clusters. The 14 medication categories were BZDs, antipsychotics, antidepressants, antimanic agents, CCBs, diuretics, RAAS inhibitors, opioids, muscle relaxants, NSAIDs, antithrombotics, steroids, anticholinergics, and other CNS drugs. All medication categories were binary variables that denoted whether the participant was taking the medication or not.

Table 6.1 Fourteen high-risk medication categories, ELSA 2012

Category	Medication	Code
BZDs	Sedatives: BZD and non-BZD derivatives	04.01.01
	Anxiolytic: lorazepam and diazepam	04.01.02
	Antiepileptic: lorazepam and diazepam	04.08.02
Antipsychotics	Atypical antipsychotics	04.02.01
	Typical antipsychotics	04.02.02
	Tourette's syndrome: sulpiride	04.09.03
Antidepressants	TCAs	04.03.01
	SSRIs	04.03.03
	SNRIs	04.03.04
Antimanic agents	Lithium and carbamazepine	04.02.03
CCBs	Both dihydropyridines and non-dihydropyridines	02.06.02
Diuretics	Thiazide-like diuretics	02.02.01
	Loop diuretics	02.02.02
	Potassium-sparing diuretics	02.02.03
	Combination: potassium-sparing + thiazide/loop	02.02.04
RAAS inhibitors	ACEIs	02.05.51
	ARBs	02.05.52
	Renin inhibitors	02.05.53
Opioids for pain relief	Opioid derivatives	04.07.02
Muscle relaxants	Quinine, diazepam, and baclofen	10.02.02
NSAIDs[§]	Including aspirin	10.01.01
Antithrombotics	Anticoagulants	02.08.02
	Anti-platelets	02.09.00
Steroids[§]	Hormone therapy: hydrocortisone	06.03.01
	Hormone therapy: prednisolone	06.03.02
	Pulmonary: prednisolone	03.01.00
	Pulmonary: hydrocortisone	06.03.02
	Inflammatory bowel disease: prednisolone and hydrocortisone	01.05.02
	Rheumatic disease: prednisolone	10.01.02

Table 6.1 (continued)

Category	Medication	Code
Anticholinergics[#]	Urinary incontinence: oxybutynin, trospium chloride, and solifenacin	07.04.02
	Smoking cessation aid Nicotine replacement therapy (all forms)	04.10.02
	Parkinson's disease: procyclidine	04.09.02
Other CNS drugs	Migraine/headache: analgesics	04.07.04
	Epilepsy: anticonvulsants	04.08.01
	Trigeminal neuralgia: anticonvulsants	04.07.03
	Parkinson's disease: carbidopa-levodopa	04.09.01
	Alzheimer's disease: Acetylcholinesterase inhibitor: donepezil Glutamate receptor antagonist: memantine	04.11.00
	Dry mouth: pilocarpine	12.03.05
	Attention deficit hyperactivity disorder: methylphenidate	04.04.00
	Alcohol dependence	04.10.01

[§] Oral form only.

[#] Remaining anticholinergics not included in other medication categories.

6.2.3 Mortality data

As explained in section 5.2 in chapter 5, study participants were linked to the NHS's Central Register. For each deceased participant up to the end of follow-up (April 2018), the month and year of death were recorded. For participants with no record of an event, the data was censored at the end of May 2018. The causes of death were classified based on the International Classification of Diseases and categorised into CVD (codes I00–I99) and non-CVD, including cancer (codes C00–C97), diseases of the respiratory system (codes J00–J99), and other remaining causes.

6.2.4 Potential confounders

The same socio-demographic characteristics and health factors were employed in this study as in chapter 5 (see section 5.2). The socio-demographic characteristics were a continuous variable of age (years), binary variables of gender (male and female) and cohabiting status (living or not with a partner), and a categorical variable of total wealth (quintiles). Health factors included six long-term conditions (diabetes mellitus, CHD, stroke, lung disease (including asthma), Parkinson's disease, and dementia (including Alzheimer's disease)), an illness count of the remaining conditions (e.g. hypertension and psychiatric conditions), functional impairment (difficulty in ADLs or IADLs), mobility difficulty, obesity (high BMI and waist circumference, and either high BMI or high waist circumference), smoking status (i.e. whether a current smoker or not), sleep duration (seven to nine hours, versus less than seven or over nine hours), low physical activity, cognitive function (scores of zero to 20), and significant depressive symptoms (four or more symptoms on the CES-D).

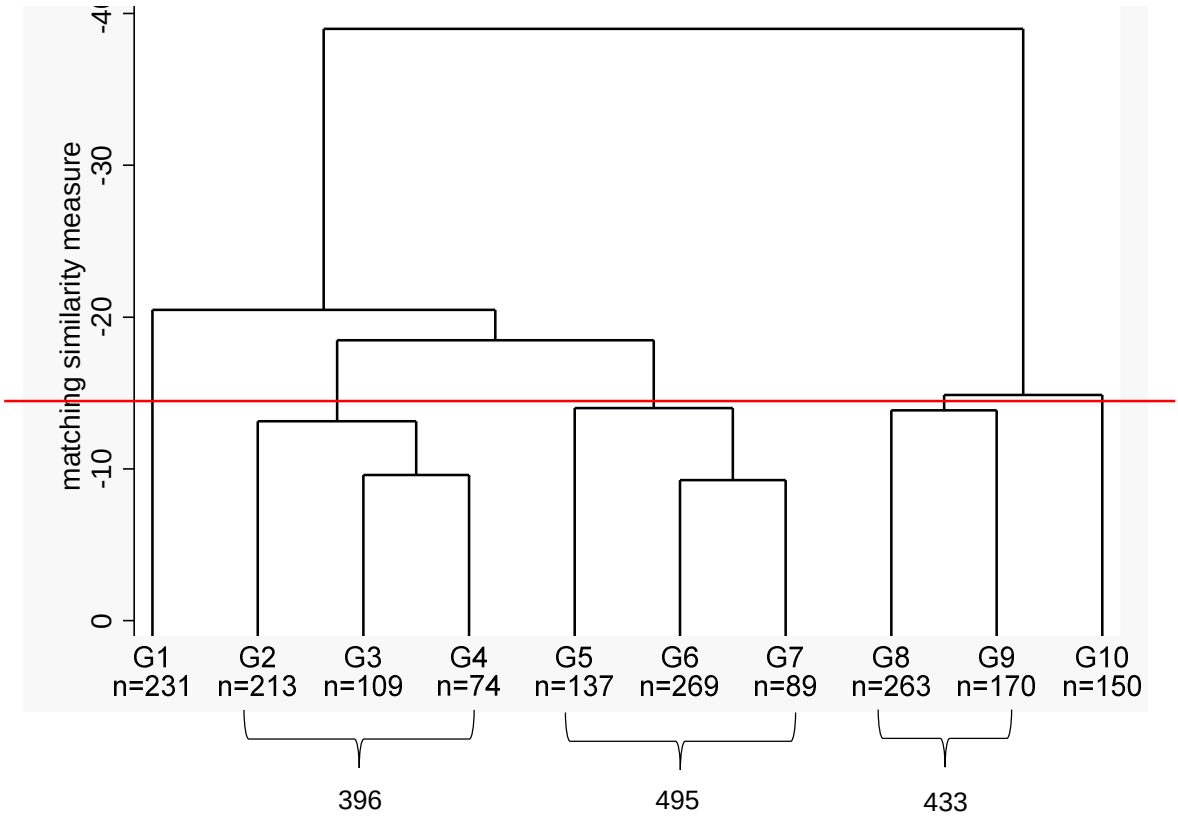
6.2.5 Statistical analysis

Cluster analysis

Cluster analysis is a useful statistical method when little is known about whether high-risk medications contribute to an increased risk of mortality among older people with polypharmacy. Cluster analysis is a method to classify a study sample based on the similarity among measured variables within clusters (groups) while maximising the dissimilarity between clusters (groups) (Everitt et al. 2011). An agglomerative hierarchical clustering approach, with Ward's linkage and the simple matching coefficient, was employed to group participants by taking account of similarity among

the 14 medication categories. Agglomerative hierarchical methods begin with each observation in its own group; then the two closest (most similar) groups are combined (all the rest of the groups remain single), and this is done repeatedly until the desired number of clusters is reached (Reed College n.d.). Ward's linkage method is also known as the minimum sum of squares, in which the lowest sum of squared distances is chosen to be combined (Everitt et al. 2011). Ward's linkage method distributes participants into clusters equivalently, whereas some methods (e.g. single linkage and complete linkage) do not converge, and other methods (e.g. weighted-average linkage and median linkage) bring about a huge gap in the sizes of clusters. The simple matching coefficient is the most common method when binary data is used in cluster analysis, along with the Jaccard coefficient and the Russell and Rao coefficient (Mooi, Sarstedt, and Mooi-Reci 2018). However, the latter two coefficients did not work well. In light of the study sample size (N = 1705), a maximum of 10 clusters was advisable in order to obtain sufficient statistical power in each cluster. The dendrogram of the 10 clusters is shown in Figure 6.1, where the proximity of clusters is explicitly presented. In cases where the clusters showed any differences in mortality, fewer clusters were chosen in order to allow each cluster to have a large enough sample to ensure a higher statistical power. The results indicated that five clusters (named clusters 1−5) fitted the data the best. The clusters were labelled based on the most prevalent medication within each cluster (80% or more); if this was not applicable, the labelling was based on the medication category with the highest prevalence across the clusters.

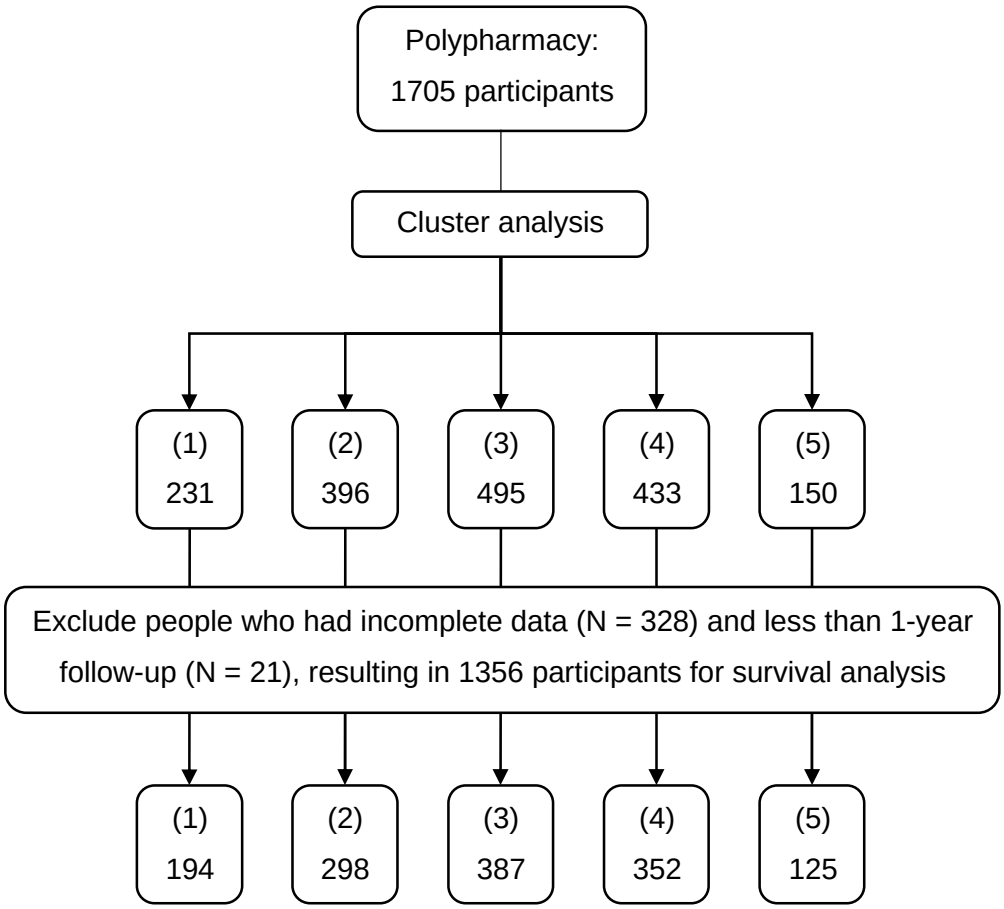
Figure 6.1 Dendrogram of cluster analysis in people with polypharmacy



Survival analysis

Five clusters (clusters 1−5) with sample sizes of 194, 298, 387, 352, and 125 respectively were employed in the survival analysis (Figure 6.2). The association between the five clusters (medication patterns) and all-cause mortality was assessed by Cox proportional hazards regression. The HRs and corresponding 95% CIs from the Cox regression and the cumulative hazard functions of clusters (medication patterns) were presented. A competing-risks regression based on Fine and Gray's proportional subhazards model (Fine and Gray 1999) was used to analyse cause-specific mortality, as it takes account of competing events that prevent the event of interest from occurring. This method prevents the overestimation of the risk of the main exposure (Feakins et al. 2018). The SHRs and corresponding 95% CIs from the competing-risks regression and the CIF denoting estimations of the incidence of the event were reported. The proportionality of hazards and subhazards was tested by using Schoenfeld residuals (Hess 1995; Zhang 2017), and no violation of assumptions was observed. The cluster (medication pattern) with the lowest mortality and/or largest sample size was used as the reference group. Interaction terms were investigated by performing likelihood ratio tests, comparing the model being tested and the full model including interaction terms. Statistical analyses were conducted using Stata (version 15.1; StataCorp LP, College Station, TX, USA).

Figure 6.2 Flow chart of samples for cluster and survival analyses



Sensitivity analysis

Several sensitivity analyses were performed to ensure the robustness of the main findings. The first sensitivity analysis (SA1) employed four cardiovascular-related diseases (i.e. CHD, stroke, hypertension, and other heart problems) individually rather than combining some of them into an illness count, because causes of death were classified as CVD and non-CVD mortality. The second sensitivity analysis (SA2) separated the diagnosis of psychiatric conditions from the illness count and adjusted it individually. In the third sensitivity analysis (SA3), alcohol consumption was added as a covariate to the main model, with a reduced sample size (N = 1221). The fourth sensitivity analysis (SA4) included an adjustment variable, an indicator of

inconsistency between medication use and self-reported conditions, in the main model to check whether the results were sensitive to the fact that some participants took cardiovascular or lipid-lowering medications but did not report relevant diagnoses. Lastly, the fifth sensitivity analysis (SA5) employed a Cox proportional hazards regression instead of a competing-risks regression to explore the association between medication patterns and cause-specific mortality.

6.3 Results

Prevalence of medication categories

The prevalence of 14 high-risk medication categories is shown in Table 6.2. RAAS inhibitors showed the highest prevalence (62.0%), followed by antithrombotics (56.8%), diuretics (39.3%), CCBs (37.6%), and antidepressants (22.6%). Opioids (12.9%), NSAIDs (11.8%), and other CNS drugs (10.0%) revealed similar prevalence rates among people with polypharmacy. The prevalence of the remaining medication groups was less than 10%.

Table 6.2 Prevalence of 14 high-risk medication categories in people with polypharmacy (N = 1356), ELSA 2012

Medication category	% (N)
BZDs*	5.6 (76)
Antipsychotics	1.1 (15)
Antidepressants	22.6 (307)
Antimanic agents	0.3 (4)
CCBs	37.6 (510)
Diuretics	39.3 (533)
RAAS inhibitors	62.0 (841)
Opioids for pain relief	12.9 (175)

Table 6.2 (continued)

Medication category	% (N)
Muscle relaxants	6.1 (82)
NSAIDs[§]	11.8 (160)
Antithrombotics	56.8 (770)
Steroids[§]	6.0 (81)
Anticholinergics[#]	5.5 (75)
Other CNS drugs	10.0 (136)

[*] Including sedatives.

[§] Oral form only.

[#] Remaining anticholinergics not included in other medication categories.

Medication pattern clusters

Based on the 14 high-risk medication categories, five clusters (medication patterns) were identified among people with polypharmacy. The distribution of medication categories across the five clusters is displayed in Figure 6.3.

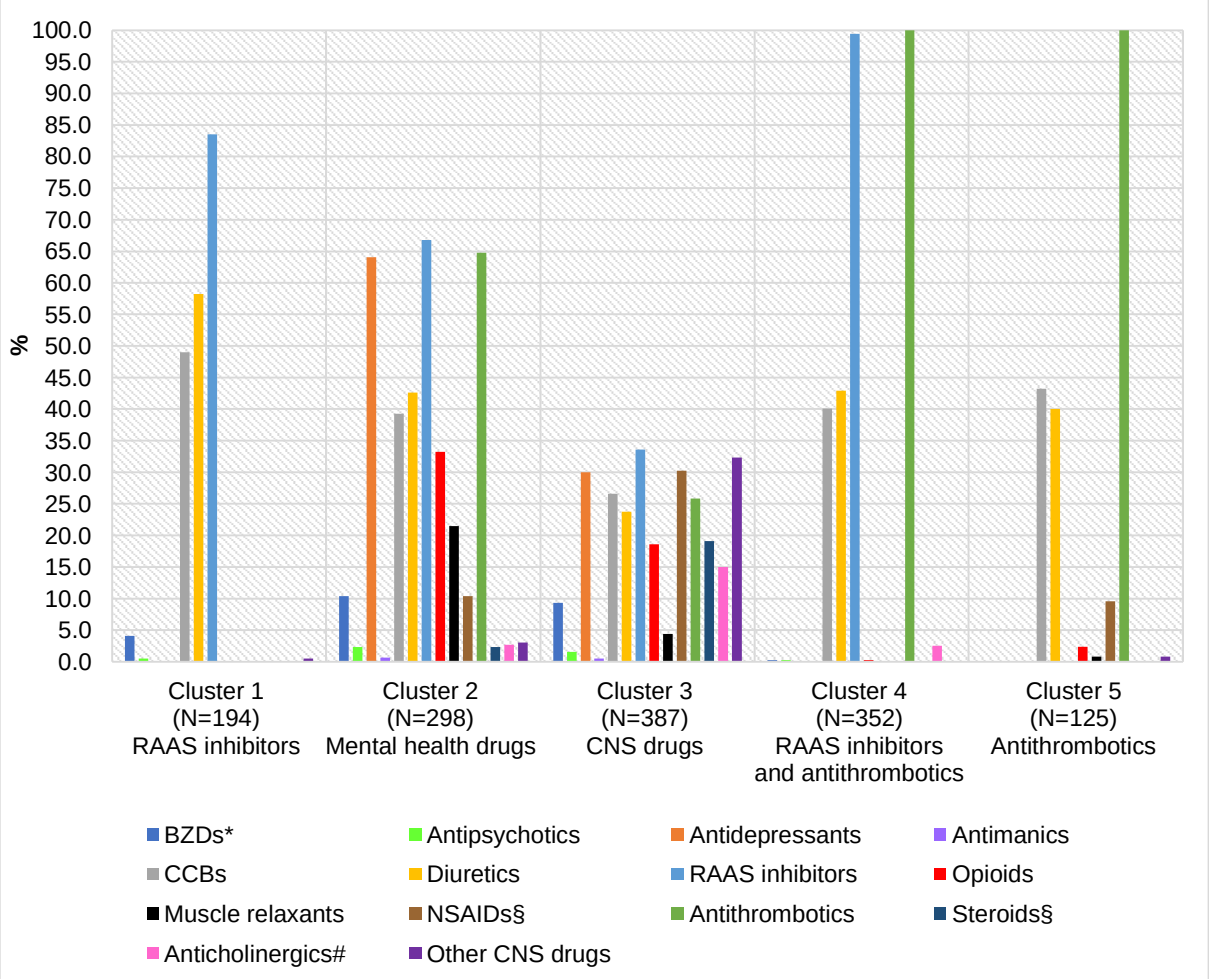
- Cluster 1 consisted of 194 participants who were frequent users of RAAS inhibitors (83.5%), diuretics (58.3%), and CCBs (49.0%). Therefore, cluster 1 was labelled ‘RAAS inhibitors’ according to the labelling method introduced in the section 6.2.
- Cluster 2 comprised 298 individuals, of whom over half took RAAS inhibitors (66.8%), antithrombotics (64.8%), and antidepressants (64.1%). This cluster also had the highest prevalence of BZDs (10.4%), antipsychotics (2.4%), and antimanic medications (0.7%), and it therefore was labelled ‘mental health drugs’.
- Cluster 3 consisted of 387 people who did not demonstrate a clear trend in the use of any specific medications. Only four medication categories had a

prevalence of 30% or more: RAAS inhibitors (33.6%), other CNS drugs (32.3%), NSAIDs (30.2%), and antidepressants (30.0%). This cluster was labelled ‘CNS drugs’ because it had the highest prevalence of other CNS drugs compared with other clusters.

- Cluster 4 comprised 352 individuals who made combined use of RAAS inhibitors and antithrombotics (99.4% and 100.0%). Approximately 40% of these participants were on diuretics and CCBs, while only a few took any of the remaining medication categories. As a result, this cluster was labelled ‘RAAS inhibitors and antithrombotics’.
- Cluster 5 consisted of 125 users of antithrombotics (100.0%), of whom 43.2% used CCBs and 40.0% used diuretics. It was therefore labelled ‘antithrombotics’.

Among the five clusters, three medication patterns − the RAAS inhibitors cluster, the RAAS inhibitors and antithrombotics cluster, and the antithrombotics cluster − were more cardiovascular-oriented, where four medication categories –CCBs, diuretics, RAAS inhibitors, and antithrombotics – were mainly involved. On the other hand, the mental health drugs cluster and the CNS drugs cluster showed a broad spectrum of medication groups, although some of them had a low prevalence. The mental health drugs cluster showed higher prevalence rates than the CNS drugs cluster in medications for mental illness (e.g. antidepressants, 64.1% versus 30.0%), cardiovascular medications (e.g. RAAS inhibitors, 66.8% versus 33.6%), opioids (33.2% versus 18.6%), and muscle relaxants (21.5% versus 4.4%). In contrast, the CNS drugs cluster had higher proportions of NSAIDs (30.2%), steroids (19.1%), anticholinergics (15.0%), and other CNS drugs (32.3%) than the mental health drugs cluster.

Figure 6.3 Prevalence of 14 high-risk medication categories across clusters, ELSA 2012



* Including sedatives.

§ Oral form only.

Remaining anticholinergics not included in other medication categories.

Sample characteristics across medication patterns

The baseline characteristics of these participants according to the five medication patterns are summarised in Table 6.3. For simplicity, results for four variables that had similar proportions across the five clusters (total wealth and cognitive function) or low prevalence (Parkinson's disease and dementia) are presented in Appendix E-1. The antithrombotics cluster was characterised by people with the highest average age

(mean age 75.2 years), and the CNS drugs cluster had the highest proportion of women (63.6%). Different clusters showed the highest prevalence of different long-term conditions: diabetes (46.9%) in the RAAS inhibitors cluster, CHD (43.5%) in the RAAS inhibitors and antithrombotics cluster, stroke (20.1%) in the mental health drugs cluster, lung disease (43.4%) in the CNS drugs cluster, and the largest number of remaining conditions (median four) in the mental health drugs cluster. Both the mental health drugs cluster and the CNS drugs cluster revealed a higher prevalence of functional impairment (52.0% versus 52.5%), mobility difficulty (88.9% versus 83.5%), current smokers (16.8% versus 16.5%), low physical activity (48.0% versus 42.9%), and significant depressive symptoms (30.2% versus 24.6%) than the other clusters.

The information on all-cause and cause-specific mortality for the five medication patterns is summarised in Table 6.4. The smallest percentage of all-cause (12.9%) and CVD mortality (4.1%) was observed in the CNS drugs cluster, but the lowest non-CVD mortality (8.2%) appeared in the RAAS inhibitors and antithrombotics cluster. By contrast, the highest prevalence of all-cause (24.0%) and non-CVD mortality (16.0%) was detected in the antithrombotics cluster, while the mental health drugs cluster showed the highest CVD mortality (10.4%). The CNS drugs cluster was therefore treated as the reference group, because it had the largest sample size and the lowest all-cause and CVD mortality.

Table 6.3 Baseline characteristics[†] of people with polypharmacy (N = 1356) by cluster, ELSA 2012

	Cluster 1 RAAS inhibitors (N = 194) % (N)	Cluster 2 Mental health drugs (N = 298) % (N)	Cluster 3 CNS drugs (N = 387) % (N)	Cluster 4 RAAS inhibitors + antithrombotics (N = 352) % (N)	Cluster 5 Antithrombotics (N = 125) % (N)
Age (years) mean (SD)	70.9 (8.2)	71.3 (9.4)	70.3 (8.5)	73.4 (8.2)	75.2 (8.3)
Women	53.6 (104)	61.1 (182)	63.6 (246)	41.8 (147)	52.8 (66)
Living with a partner	71.1 (138)	56.7 (169)	64.9 (251)	63.9 (225)	52.8 (66)
Diabetes mellitus	46.9 (91)	37.9 (113)	25.1 (97)	37.2 (131)	32.8 (41)
CHD	12.9 (25)	38.3 (114)	14.2 (55)	43.5 (153)	39.2 (49)
Stroke	4.1 (8)	20.1 (60)	7.0 (27)	14.8 (52)	15.2 (19)
Lung disease (including asthma)	33.5 (65)	28.2 (84)	43.4 (168)	20.7 (73)	26.4 (33)
Number of conditions[#] median (IQR)	3 (2)	4 (2)	3 (2)	3 (2)	3 (2)
Functional impairment[§]	26.8 (52)	52.0 (155)	52.5 (203)	28.7 (101)	29.6 (37)
Mobility difficulty[*]	68.6 (133)	88.9 (265)	83.5 (323)	71.6 (252)	84.0 (105)
Obesity					
High BMI and waist circumference	50.5 (98)	49.3 (147)	40.1 (155)	38.4 (135)	40.0 (50)
Either high BMI or high waist circumference	26.8 (52)	25.2 (75)	24.0 (93)	27.3 (96)	28.0 (35)
Current smoker	11.3 (22)	16.8 (50)	16.5 (64)	9.4 (33)	5.6 (7)
Sleep < 7 or > 9 hours	38.7 (75)	46.6 (139)	53.8 (208)	39.2 (138)	49.6 (62)
Low physical activity	29.4 (57)	48.0 (143)	42.9 (166)	31.8 (112)	38.4 (48)
Depressive symptoms 4+	7.7 (15)	30.2 (90)	24.6 (95)	11.9 (42)	11.2 (14)

Table 6.3 (footnotes)

[†] All characteristics showed significantly different proportions among the five clusters. Two variables (total wealth and cognitive function) with similar distributions across the five clusters and two conditions (Parkinson's disease and dementia (including Alzheimer's disease)) with low prevalence rates are shown in Appendix E-1.

[#] The remaining other conditions, not including diabetes mellitus, CHD, lung disease, Parkinson's disease, and dementia (including Alzheimer's disease).

[§] Defined as any difficulty in either ADLs or IADLs.

[*] Defined as any difficulty in the movement of the arms or lower limbs.

Table 6.4 Mortality[†] in people with polypharmacy (N = 1356) by cluster, ELSA 2018

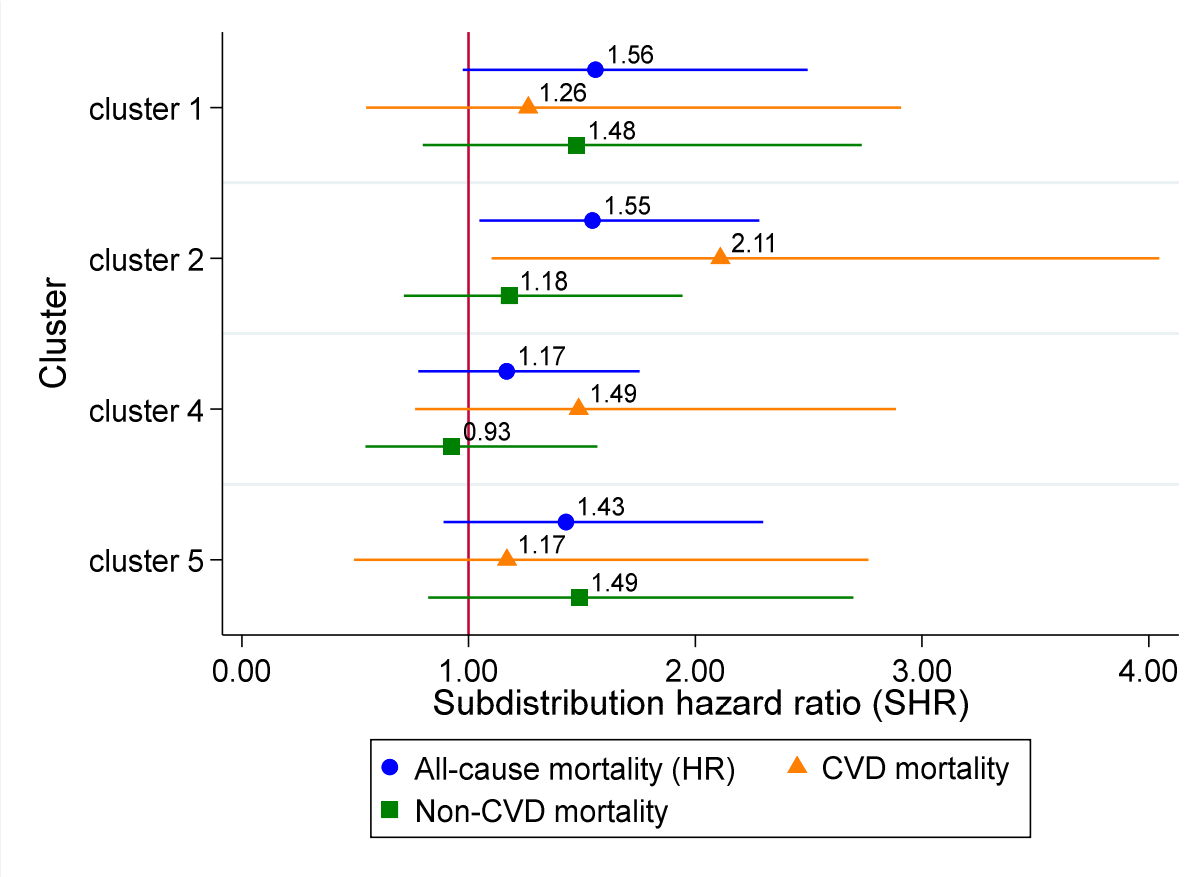
	Cluster 1 RAAS inhibitors (N = 194) % (N)	Cluster 2 Mental health drugs (N = 298) % (N)	Cluster 3 CNS drugs (N = 387) % (N)	Cluster 4 RAAS inhibitors + antithrombotics (N = 352) % (N)	Cluster 5 Antithrombotics (N = 125) % (N)
All-cause mortality	15.5 (30)	22.2 (66)	12.9 (50)	16.8 (59)	24.0 (30)
CVD mortality	4.6 (9)	10.4 (31)	4.1 (16)	8.5 (30)	8.0 (10)
Non-CVD mortality	10.8 (21)	11.7 (35)	8.8 (34)	8.2 (29)	16.0 (20)

[†] Data was collected before May 2018.

The impact of medication patterns on mortality

Figure 6.4 shows the results of the association between medication patterns (at baseline in 2012) and mortality (up to 2018). All-cause mortality was analysed by Cox proportional hazards regressions with corresponding HRs and 95% CI, and cause-specific mortality was assessed using a competing-risks regression that reported SHR and 95% CI. Over the six-year follow-up, only the mental health drugs cluster (cluster 2) showed a raised risk of all-cause mortality (HR = 1.55, 95% CI = 1.05, 2.28, p = 0.028) and CVD mortality (SHR = 2.11, 95% CI = 1.10, 4.05, p = 0.024) compared with the CNS drugs cluster (cluster 3). Neither the RAAS inhibitors cluster (cluster 1), the RAAS inhibitors and antithrombotics cluster (cluster 4), nor the antithrombotics cluster (cluster 5) revealed any differences in all-cause, CVD, or non-CVD mortality. The cumulative hazard function of all-cause mortality and the CIF of CVD mortality for the five medication patterns are presented in Figure 6.5. Diabetes was not an effect modifier in the association between medication patterns and mortality, since no significant interactions between diabetes and other covariates were identified by the likelihood ratio tests. After other factors were accounted for, diabetes was not found to be an independent risk factor for all-cause or cause-specific mortality in this study.

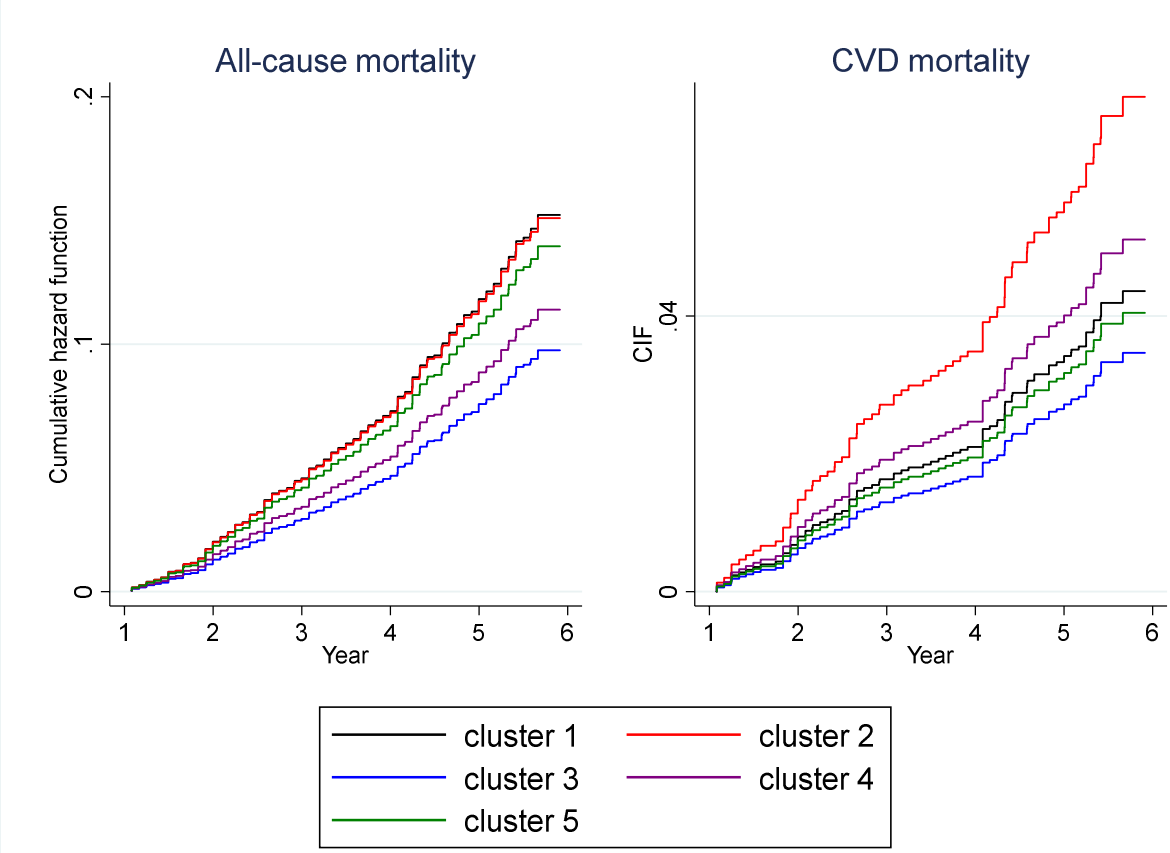
Figure 6.4 Associations[#] between medication patterns[*] and mortality in people with polypharmacy in England in 2012−18



[#] Adjusted for age, gender, cohabitation, wealth, six long-term conditions (diabetes, CHD, stroke, lung disease, Parkinson's disease, and dementia (including Alzheimer's disease)), an illness count of the remaining conditions, functional impairment, mobility difficulty, obesity, smoking status, sleep duration, low physical activity, cognitive function, and depressive symptoms.

[*] Cluster 1 = RAAS inhibitors cluster; cluster 2 = mental health drugs cluster; cluster 3 = CNS drugs cluster (reference); cluster 4 = RAAS inhibitors and antithrombotics cluster; cluster 5 = antithrombotics cluster.

Figure 6.5 Cumulative hazard function of all-cause mortality and CIF of CVD mortality for five medication patterns* in people with polypharmacy in England in 2012−18



* Cluster 1 = RAAS inhibitors cluster; cluster 2 = mental health drugs cluster; cluster 3 = CNS drugs cluster (reference); cluster 4 = RAAS inhibitors and antithrombotics cluster; cluster 5 = antithrombotics cluster.

Sensitivity analysis

The results of the sensitivity analyses are summarised in Appendix E-2. The first sensitivity analysis (SA1) individually adjusted for each cardiovascular-related diagnosis – i.e. CHD, stroke, hypertension, and other heart problems – and obtained similar findings to the primary analysis (the mental health drugs cluster: HR = 1.53 versus 1.55 for all-cause mortality, SHR = 2.10 versus 2.11 for CVD mortality). SA2 adjusted for psychiatric conditions separately, and the results remained the same (the

mental health drugs cluster: HR = 1.54 for all-cause mortality, SHR = 2.13 for CVD mortality). SA3 additionally included alcohol consumption, with a reduced sample size (N = 1221). The associations were unchanged, although the estimates of the risk of mortality for the mental health drugs cluster were slightly higher than those found in the primary analysis, with 1.70 versus 1.55 for all-cause mortality, and 3.04 versus 2.11 for CVD mortality. In the fourth sensitivity analysis (SA4), an indicator of inconsistency between medication use and self-reported conditions was added to the main model. This indicator aimed to adjust for long-term conditions as comprehensively as possible by taking account of people on cardiovascular or lipid-lowering medications but without relevant diagnoses (9.6%). The findings were similar to the primary analysis after adjustment for the indicator (the mental health drugs cluster: HR = 1.54 versus 1.55 for all-cause mortality, SHR = 2.03 versus 2.11 for CVD mortality). Lastly, SA5 was only done for CVD and non-CVD mortality, and the Cox proportional hazards regression was employed instead of a competing-risks regression. The results were similar between the two statistical methods, although the estimates with the Cox regression were generally greater than those with the competing-risks regression, with 2.16 versus 2.11 for CVD mortality, and 1.35 versus 1.18 for non-CVD mortality. This situation supports the notion that taking competing events into account can avoid the overstatement of risks (Feakins et al. 2018) or inappropriate estimations when there is a greater association between competing causes of death (Collett 2015); consequently, it justified the primary analysis.

6.4 Discussion

6.4.1 Summary

Among people with polypharmacy, five high-risk medication patterns − a RAAS inhibitors cluster, a mental health drugs cluster, a CNS drugs cluster, a RAAS inhibitors and antithrombotics cluster, and an antithrombotics cluster – were identified using an agglomerative hierarchical clustering method. Over the six-year follow-up, the mental health drugs cluster showed increased risks of all-cause mortality (HR = 1.55) and CVD mortality (SHR = 2.11) compared with the CNS drugs cluster, while none of the other medication patterns (single or combined use of RAAS inhibitors and antithrombotics) showed differences in mortality. Apart from medications for mental illness and CVD, the mental health drugs cluster also had a higher prevalence of opioids (33.2% versus 18.6%) and muscle relaxants (21.5% versus 4.4%) than the CNS drugs cluster. These findings suggest that older adults with polypharmacy who take medication for mental disorders (primarily antidepressants), opioids, and muscle relaxants have added risks of all-cause and CVD mortality when their polypharmacy status is positively associated with mortality. The robustness of the main findings was largely confirmed by the sensitivity analyses.

The mechanisms that account for the increased risk of mortality with mental health drugs, opioids, and muscle relaxants among people with polypharmacy may potentially involve drug-drug interactions or comorbidities. Antidepressants that include TCAs, SSRIs, and SNRIs have shown many pharmacokinetic and pharmacodynamic interactions with other medications, and some of these are of clinical significance (Bleakley 2016). Serotonin syndrome is one of the common consequences of drug-drug interactions and has a wide spectrum of symptoms, from

the mild (diarrhoea or tremor) to the life-threatening (ataxia or convulsions) (Bleakley 2016). For example, antidepressants in combination with fentanyl (long-acting opioids) or lithium (antimanic agents) are likely to promote serotonin syndrome. Older people on antidepressants have also been confirmed to have a higher number of comorbidities; therefore, a higher proportion of people have at least one potential treatment conflict between other conditions (e.g. CVD and arthritis or pain management) and antidepressants (Caughey et al. 2010).

Similarly, major potential drug-drug interactions between opioids and other medications have been reported where opioids are frequently prescribed with antifungal agents, antibiotics, CCBs, antiarrhythmics, SSRIs, or anticonvulsants for chronic pain opioid users (Pergolizzi et al. 2014). In the mental health drugs cluster, 33.2% were opioid users, and such interactions could have had a major clinical influence. Opioid prescription at discharge from hospital has also been found to be related to the greater illness burden (i.e. higher multimorbidity severity) among hospitalised older people (Schear et al. 2019). In addition, a study of breast cancer survivors provided a link between mental disorders and opioid use, implying that this association might be present among older adults as well (Desai et al. 2019).

There are also concerns about drug-drug interactions with muscle relaxants, including quinine, diazepam, and baclofen (Kral and Ustic 2012). However, there has been no systematic discussion of the drug-drug interactions of muscle relaxants because they include diverse drug classes. Both opioids and muscle relaxants are commonly prescribed for pain management, and they both simultaneously showed the highest prevalence in the mental health drugs cluster. To summarise, the use of antidepressants and opioids may lead to clinically important drug-drug interactions and treatment conflicts with conditions. This situation is likely to be more complicated

and unpredictable for older adults with polypharmacy and may account for the increased mortality in the mental health drugs cluster.

6.4.2 Comparison with existing literature

To date and to my knowledge, this was the first study to investigate the association between high-risk medication patterns and mortality among older adults with polypharmacy; thus, direct comparisons with previous studies are difficult to make.

In the literature, only all-cause mortality has been widely explored, rather than cause-specific mortality. The finding concerning the relationship between mental health drugs and mortality is supported by the literature (Gill et al. 2007; Weinmann, Read, and Aderhold 2009; Makris et al. 2015), although some studies have focused on exposure to antipsychotics in schizophrenia patients (Weinmann, Read, and Aderhold 2009) or older adults with dementia (Gill et al. 2007). The finding that opioids are associated with higher mortality is also in line with previous literature (Glynn et al. 2001; Makris et al. 2015; Ray et al. 2016), including samples of people with chronic non-cancer pain (Makris et al. 2015; Ray et al. 2016) or at least one hospitalisation during the study period (Glynn et al. 2001). However, some differences between this study and the previous literature can be observed. The use of muscle relaxants was linked to increased mortality in this study, while previous studies have shown a lower risk (Makris et al. 2015). Also, this study did not find an association between anticholinergics and mortality, whereas the use of anticholinergics has shown a higher risk of mortality in previous studies (Ruxton, Woodman, and Mangoni 2015; Sarbacker et al. 2017; Hanlon et al. 2020). The difference in the medication classifications used may explain the lack of association in this study. This study adopted 14 high-risk medication categories based on their pharmacological mechanisms (e.g.

antidepressants and the remaining anticholinergics), whereas the anticholinergic cognitive burden scale in the literature has included wide-ranging drug classes such as paroxetine (an antidepressant), diazepam (a BZD), warfarin (an antithrombotic agent), fentanyl (an opioid), and nifedipine (a CCB) (Campbell et al. 2013).

Furthermore, the impact of medications on all-cause mortality has usually been analysed in previous literature by using separate models for each drug class and then controlling for potential confounders. In other words, this literature has studied each drug class individually, without taking account of concurrent medications that may affect or interact with each other and subsequently influence mortality. Although this study took 14 high-risk medication categories into account concurrently, it identified the likelihood of death posed by medication patterns (combinations), rather than making causal inferences with regard to specific medications and mortality. The findings of this study emphasise that medication patterns with mental health drugs, opioids, and muscle relaxants may impose an additional risk of all-cause and CVD mortality on community-dwelling older adults with polypharmacy. Thus, this specific group of people may need more attention and prompt intervention.

6.4.3 Strengths and limitations

This study had several strengths. First, the medication profiles were collected by nurses rather than self-reported by participants, and they were used to verify the self-reported health conditions. This verification and collection process helped to reduce misreporting bias. Second, a rigorous definition of polypharmacy was chosen that included medications in long-term use and excluded the temporary use of painkillers. Third, OTC medications for long-term conditions were also included, since some interactions between OTC and prescribed medications might be a concern. Fourth,

the study employed a nationally representative sample followed up for six years, for whom comprehensive characteristics were available ranging from socio-demographic characteristics to health status. Fifth, a wider range of potential confounders was adjusted for statistically than in previous research, including cognitive function, mobility impairment, lifestyle factors, and depressive symptoms. Lastly, this study used advanced statistical techniques – cluster analysis and survival analysis – to investigate the association between high-risk medications and mortality. Given the data-driven nature of the clustering approach, different clusters of participants could be identified using different sets of medication groups or different samples. However, similar medication patterns are likely to be found when the same groups of medications are employed as in this study. Competing-risks analysis was used for cause-specific mortality to take account of the event of interest and competing events simultaneously, and thus the estimates should be more accurate.

Some limitations of this study should also be acknowledged. Information was collected during the nurse visits on medication type but not on duration, dose, or frequency. Also, the medication collection was made at a single time point, and the medicines may have changed over the follow-up period, so immeasurable time bias could not be avoided (Suissa 2008). Lastly, the lack of a significant association between cause-specific mortality and the medication patterns might be due to low statistical power, attributable to the small number of deaths. More research with a large sample is warranted to confirm the lack of association between medication patterns and cause-specific mortality.

6.5 Conclusion

The concurrent use of mental health drugs (primarily antidepressants), opioids, and muscle relaxants was found to increase the risk of all-cause and CVD mortality, compared with other medication patterns, among older people with polypharmacy in England. This supports that addictive pain management medications should be included in the structured medication reviews of older adults with polypharmacy, but it also suggests that the prescription of mental health medications and muscle relaxants may need more attention. The reinforcement of structured medication reviews would contribute to early intervention in medication use, and it may help to reduce polypharmacy-related problems and bring clinical benefits to older people.

Chapter 7. Discussion

This PhD research aimed to investigate a broad range of polypharmacy issues in community-dwelling older adults. The four main objectives of this study were:

1. To report the prevalence of diagnosed and undiagnosed diabetes between 2004 (Wave 2) and 2012 (Wave 6) and the risk factors for undiagnosed diabetes.
2. To investigate the prevalence of and risk factors for polypharmacy according to diabetes status.
3. To study the association between different levels of polypharmacy and all-cause and cause-specific mortality.
4. To explore the association between high-risk medications and all-cause and cause-specific mortality among older adults with polypharmacy.

The four objectives were accompanied by four hypotheses:

1. It was hypothesised that the prevalence of undiagnosed diabetes had decreased over time, concomitant with improved awareness of diabetes resulting from the effort invested in both public information campaigns and screening tests in primary care in the UK over the period between 2004 and 2012.
2. It was hypothesised that diabetes contributed to the development of polypharmacy among older people, and that it might influence the potential risk factors for polypharmacy.
3. It was hypothesised that a gradient relationship existed between different levels of polypharmacy and all-cause and cause-specific mortality among older adults, independently of health status.

4. It was hypothesised that some high-risk medications might further increase the risk of mortality in older adults with polypharmacy.

Four studies were carried out to address these objectives. The findings of each study, overall strengths and limitations, and clinical and research implications of this PhD work are discussed in this chapter, together with future plans and a final conclusion.

7.1 Summary of main findings

The aim of the first study was to investigate the change in the prevalence of diagnosed and undiagnosed diabetes between 2004 and 2012 and to analyse the risk factors for undiagnosed diabetes. The overall prevalence of diagnosed (7.7% versus 11.5%) and undiagnosed (2.4% versus 3.4%) diabetes increased in this period, with a slight improvement in the awareness of people with diabetes (unawareness proportions 17.3% versus 29.2%). The growing prevalence of undiagnosed diabetes contradicted the hypothesis, whereas the improved awareness of diabetes confirmed it. Diagnosed diabetes showed an increasing trend over time for men and women in different age groups; however, this was not the case with undiagnosed diabetes. Men aged 50–74 had a stable prevalence of undiagnosed diabetes (3.2% versus 2.3%), but there was a significant decline in the proportion of men with diabetes who were unaware of their condition (29.2% versus 17.3%). Women in all age groups and men aged 75+ showed an increasing prevalence of undiagnosed diabetes and a growing proportion of people who were unaware of their condition.

The second study aimed to understand whether having diabetes (in both diagnosed and undiagnosed cases) was related to the prevalence of and risk factors

for polypharmacy among older people. The results showed that people with diabetes had a substantially higher prevalence of polypharmacy (41.1% versus 14.8%) and heightened polypharmacy (5.8% versus 1.7%) than those without diabetes, even when medications specifically for diabetes were excluded. The results confirmed the hypothesis that diabetes was a great contributor to polypharmacy among older adults. The risk factors for polypharmacy and heightened polypharmacy in the two groups also differed. People with diabetes who were men and obese were more likely to show polypharmacy and heightened polypharmacy, while those without diabetes who had more depressive symptoms and worse cognitive function were at high risk. However, the results of this study showed for the first time that long-term conditions had a similar effect on polypharmacy in people with and without diabetes. More importantly, older age, which is regarded as a key factor for polypharmacy in the literature, was no longer associated with polypharmacy and heightened polypharmacy among older adults with diabetes after adjustments for long-term conditions and health factors.

The aim of the third study was to examine the association between different levels of polypharmacy and all-cause and cause-specific mortality. Polypharmacy and heightened polypharmacy showed a dose-response relationship with all-cause (HR = 1.51 and 2.29) and CVD (SHR = 2.45 and 3.67) mortality among older adults in England over a six-year period. The results were in line with the hypothesis of a gradient relationship between different levels of polypharmacy and mortality in older adults, independently of underlying health conditions. Heightened polypharmacy was additionally associated with cancer mortality (SHR = 3.03), even when people who had cancer at baseline were excluded. The presence of long-term conditions played the most important role in the association between polypharmacy and all-cause mortality, and diabetes was a confounder in this relationship. Diabetes, CHD, and lung

disease were also independently related to a higher risk of all-cause mortality, conditional on the same polypharmacy status.

The fourth study further explored whether high-risk medications posed a greater risk of all-cause and cause-specific mortality for older adults with polypharmacy, where polypharmacy was regarded as entailing higher mortality. Five high-risk medication patterns − a RAAS inhibitors cluster, a mental health drugs cluster, a CNS drugs cluster, a RAAS inhibitors and antithrombotics cluster, and an antithrombotics cluster – were identified in people with polypharmacy. Among these patterns, the mental health drugs cluster showed higher risks of all-cause (HR = 1.55) and CVD (SHR = 2.11) mortality than the CNS drugs cluster, while others showed no differences in mortality. The mental health drugs cluster also showed the highest prevalence of opioids and muscle relaxants among the five clusters. The findings suggested that older adults with polypharmacy who took mental health drugs (primarily antidepressants), opioids, and muscle relaxants were at higher risk of all-cause and CVD mortality, compared with those who did not take these types of medications. The results supported the hypothesis that particular high-risk medications further increased the mortality risk among older adults with polypharmacy.

To summarise, approximately one fifth of all participants were classified as having polypharmacy or heightened polypharmacy, indicating that polypharmacy was a prevalent phenomenon in this representative sample of community-dwelling older adults in England. Half of the older adults with diabetes showed polypharmacy – a considerably higher prevalence than among those without diabetes – while diagnosed and undiagnosed diabetes kept rising over time. This was the first study to evaluate polypharmacy issues according to diabetes status, and it emphasised the importance of diabetes in the development of polypharmacy. Age was no longer a risk factor for

polypharmacy among older people with diabetes, but male sex and obesity remained key features. Furthermore, polypharmacy and heightened polypharmacy showed a dose-response relationship not only with all-cause mortality but also with CVD mortality, which has never been investigated before. Diabetes acted as an independent risk factor for mortality, highlighting the importance of diabetes in the care of older people. Lastly, this was the first study to my knowledge to identify particular high-risk medications – mental health drugs, opioids, and muscle relaxants – that further increased the risk of all-cause and CVD mortality among older adults with polypharmacy. Taken together, these findings suggest that polypharmacy is prevalent among older adults in England and that it is prone to higher mortality, especially for those on mental health drugs, opioids, and muscle relaxants. Diabetes in older people makes a substantial contribution to polypharmacy and predicts mortality independently.

7.2 Strengths and limitations

The strengths and limitations of each study have already been presented at the end of each chapter. This section highlights the overall strengths of this PhD research, along with its limitations.

This PhD work has several strengths. First, polypharmacy is a legitimate response to multimorbidity, but it is also influenced by health service utilisation behaviours in some cases. Understanding the prevalence, risk factors, and health consequences of polypharmacy in a nationally representative sample of older adults (ELSA) is one of the novelties of this work. ELSA collects comprehensive information on social, economic, and health aspects from a nationally representative sample of

older adults, thus enabling the investigation of polypharmacy issues under well-considered circumstances. Second, this PhD work set up a rigorous definition of polypharmacy that included exclusively long-term medications and concurrent OTC drugs for long-term conditions or symptoms. The inclusion of OTC drugs contributed to a thorough assessment of medication use among older people. Third, medication profiles were collected by nurses and used to verify self-reported health conditions and to define specific long-term conditions (not self-reported). This verification and collection process helped to reduce misreporting bias. Fourth, the verified diagnosis of diabetes used in the second, third, and fourth studies included undiagnosed cases and further reduced misclassification bias. Lastly, this PhD work used linked observational data from ELSA with mortality data derived from national registers rather than reports from relatives or others. The NHS's Central Register provides information on not only all-cause death but broad categories of cause of death.

The limitations of this PhD work should also be acknowledged in terms of the data, study design, and methodology. The first limitation concerns data collection and the definition of polypharmacy. Information on drug duration, dose, and frequency was not collected during the nurse visits, so no definite cut-off for long-term medications could be used, nor could appropriate or problematic polypharmacy be assessed. Also, some combination medications were indistinguishable from a single medication, so the amount of polypharmacy may have been underestimated in these cases. With regard to the mortality studies, the medications were collected at a single time point and may have changed over the follow-up period; thus, unmeasured time bias could not be avoided. Repeated measurements of the medication data would have helped to exclude people with short-term polypharmacy and ensure the persistence of polypharmacy status. In that case, the positive association between polypharmacy

and death would have been more robust and not overestimated. Further, recall bias in personal interviews and self-completion questionnaires may have occurred, even though self-reported conditions were verified by medication use.

The second limitation of this work is related to the study design. The first two studies were cross-sectional studies, so causality could not be ascertained. Moreover, there may have been underlying unmeasured factors that were responsible for the associations observed in this PhD work, because observational studies are subject to the residual confounding issue. The third limitation of this PhD research relates to methodological issues. By protocol, some participants were not eligible for blood sample collection (e.g. people who had a clotting or bleeding disorder or were currently on anticoagulant drugs) (Institute for Fiscal Studies 2014). In the first study of undiagnosed diabetes, participants who had HbA1c data showed significant differences in socio-demographic characteristics and health-related features compared with those who did not have HbA1c information. It may be that the results of the first study underestimated the effects, since sicker people had been excluded during the data collection process. Furthermore, as ELSA is a longitudinal study, individuals who participated in ELSA in 2004 and had high blood sugar levels received feedback on their blood biomarkers, and they may have contacted their GPs and had diabetes diagnosed. In that case, the prevalence of undiagnosed diabetes in 2012 will have decreased accordingly. Additionally, undiagnosed diabetes was defined by a single HbA1c value, which may have led to imprecision, since a clinical diagnosis mostly needs at least two tests or symptoms.

7.3 Clinical implications

The results of this PhD research highlight the importance of greater awareness of polypharmacy among older adults living in England, and in particular of special care for older people with diabetes. As polypharmacy status and certain long-term conditions (i.e. diabetes, CHD, and lung disease) were found to increase the risk of mortality in older people, polypharmacy management may need to integrate key conditions such as diabetes. In addition, some high-risk medications were identified as posing additional mortality risk to older adults with polypharmacy, which may help to improve the strategy for dealing with polypharmacy.

Medication reviews have been recommended by NICE (NICE 2020), NHS Scotland (NHS Scotland 2020), and NHS England (NHS England and NHS Improvement 2019) as a clinical intervention in polypharmacy. NHS England's medication review service is in transition at the moment, moving away from the medicines use reviews (MURs) commissioned from community pharmacies and towards enhanced 'structured medication reviews' carried out by clinical pharmacists (Department of Health and Social Care 2020). Clinical pharmacists are recruited in primary care networks as part of the new GP contract framework. The MUR service was introduced in 2005 and ended in the 2020–21 financial year. The national target groups for MURs are patients who take a high-risk medicine, and patients who have been discharged from hospital in the previous eight weeks and had changes made to the drugs they take while in hospital. High-risk medicines in MURs refer to NSAIDs, anticoagulants, anti-platelets, and diuretics (NHS Business Services Authority 2019). The MUR service was implemented in the UK for 15 years, with an unclear impact on patients' outcomes, although both pharmacists and patients viewed MURs positively

(Stewart et al. 2020). The results of this study somewhat confirm the effectiveness of MURs in a community sample of older adults, since none of the MUR drug lists showed an association with increased mortality.

The new structured medication reviews started in April 2020 (NHS England and NHS Improvement 2019). The current proposed service model for structured medication reviews identifies certain groups of people who may benefit the most, including care home residents, people with frailty, patients with multiple comorbidities (particularly respiratory disease and CVD), patients with complex and problematic polypharmacy (specifically those on 10 or more medications), patients prescribed medicines that are commonly related to medication errors, and patients prescribed high numbers of addictive pain management drugs (NHS England and NHS Improvement 2019). The findings of this study suggest that in addition to structured medication reviews among older adults with heightened polypharmacy, those with polypharmacy should also be monitored, as they were found to be prone to adverse outcomes (i.e. mortality). This PhD work provides robust evidence of the higher risk that polypharmacy status poses in terms of not only death, but also high-risk medications which in turn increase the risk of mortality among older people with polypharmacy. Some medication use has been flagged in the polypharmacy guidance issued by NHS England and NHS Scotland. The service model of structured medication reviews proposed by NHS England includes addictive pain management drugs (e.g. opioids) (NHS England and NHS Improvement 2019), while the Scottish government has set up a long list of high-risk medications, defined by 17 case-finding indicators that refer to combinations of particular medications and specific symptoms or conditions (Scottish Government Polypharmacy Model of Care Group 2018). In the list of high-risk medications, no mental health drugs or muscle relaxants are discussed

except for lithium, but opioids at high doses and in long-term use are emphasised. This study supports the inclusion of opioids in the current guidance, but it also suggests that older adults with polypharmacy who take mental illness medications and muscle relaxants are prone to suffer from adverse outcomes and therefore may need more attention. These results are expected to improve the service model of structured medication reviews, contributing to early intervention for older adults with polypharmacy and on specific medications. Early intervention in medication use, such as the close monitoring of specific medications and regular medication reviews, would ensure treatment appropriateness and medication optimisation, reduce polypharmacy-related problems such as adverse effects, drug-drug interactions, and redundant medications, and potentially bring clinical benefits to older people with polypharmacy.

In addition to polypharmacy status and high-risk medications, this PhD work highlights the importance of diabetes, CHD, and lung disease due to the high probability of adverse outcomes. This work accordingly highlights the need to integrate key conditions into both polypharmacy management and multimorbidity management, since no specific conditions are incorporated in the multimorbidity management or medicines optimisation proposed by NICE (Figure 7.1 to Figure 7.4) (NICE 2016). More importantly, this work not only supports the current guidelines on polypharmacy management, but also contributes to the improvement and updating of the guidelines. The findings of this PhD suggest that older adults with diabetes need to receive structured medication reviews, not only because of their considerable prevalence of polypharmacy, but also due to their increased mortality risk, apart from people with respiratory disease or CVD, who have been advised to do structured medication reviews according to NHS England (NHS England and NHS Improvement 2019).

Figure 7.1 NICE interactive flow chart for multimorbidity

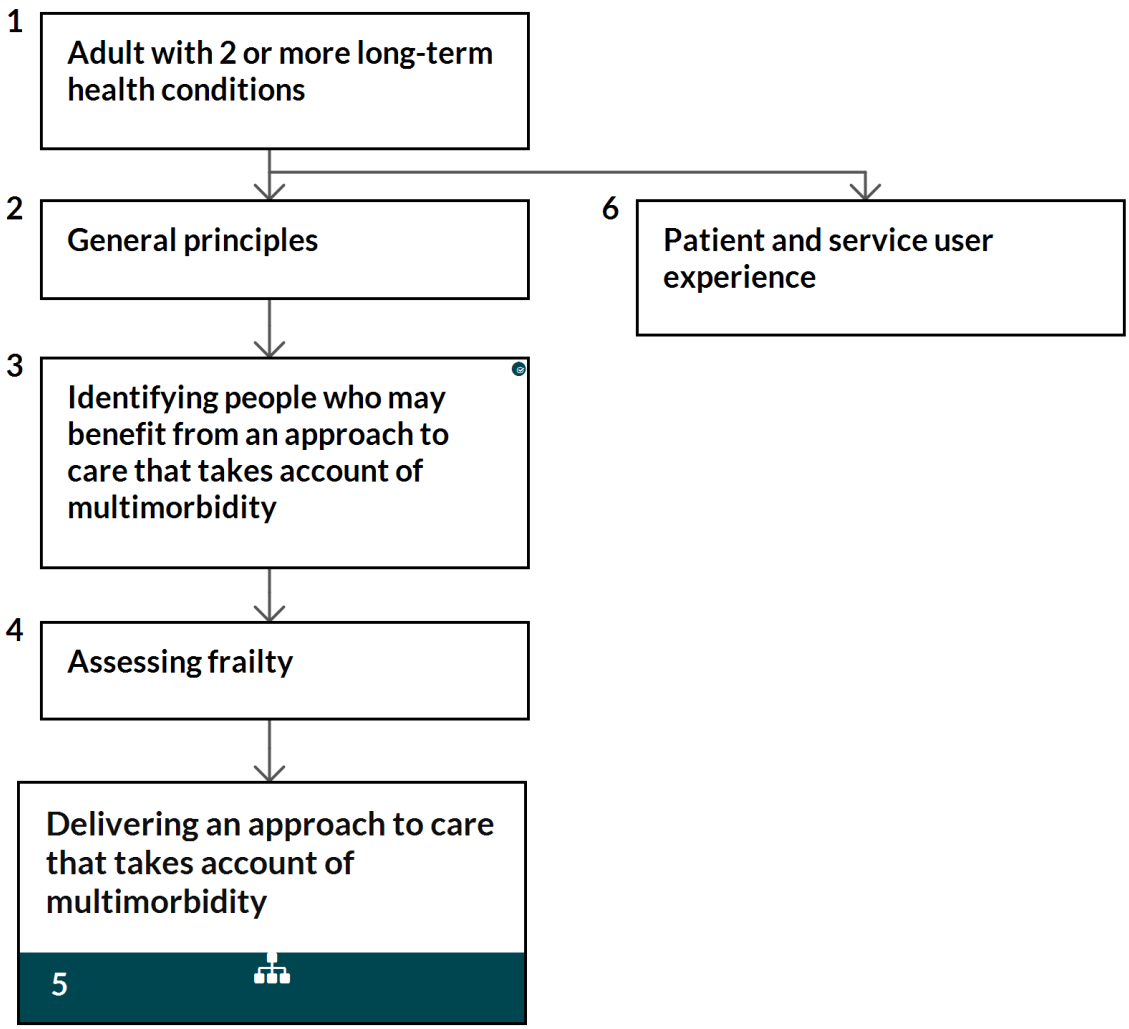


Figure 7.2 NICE interactive flow chart for delivering an approach to care that takes account of multimorbidity

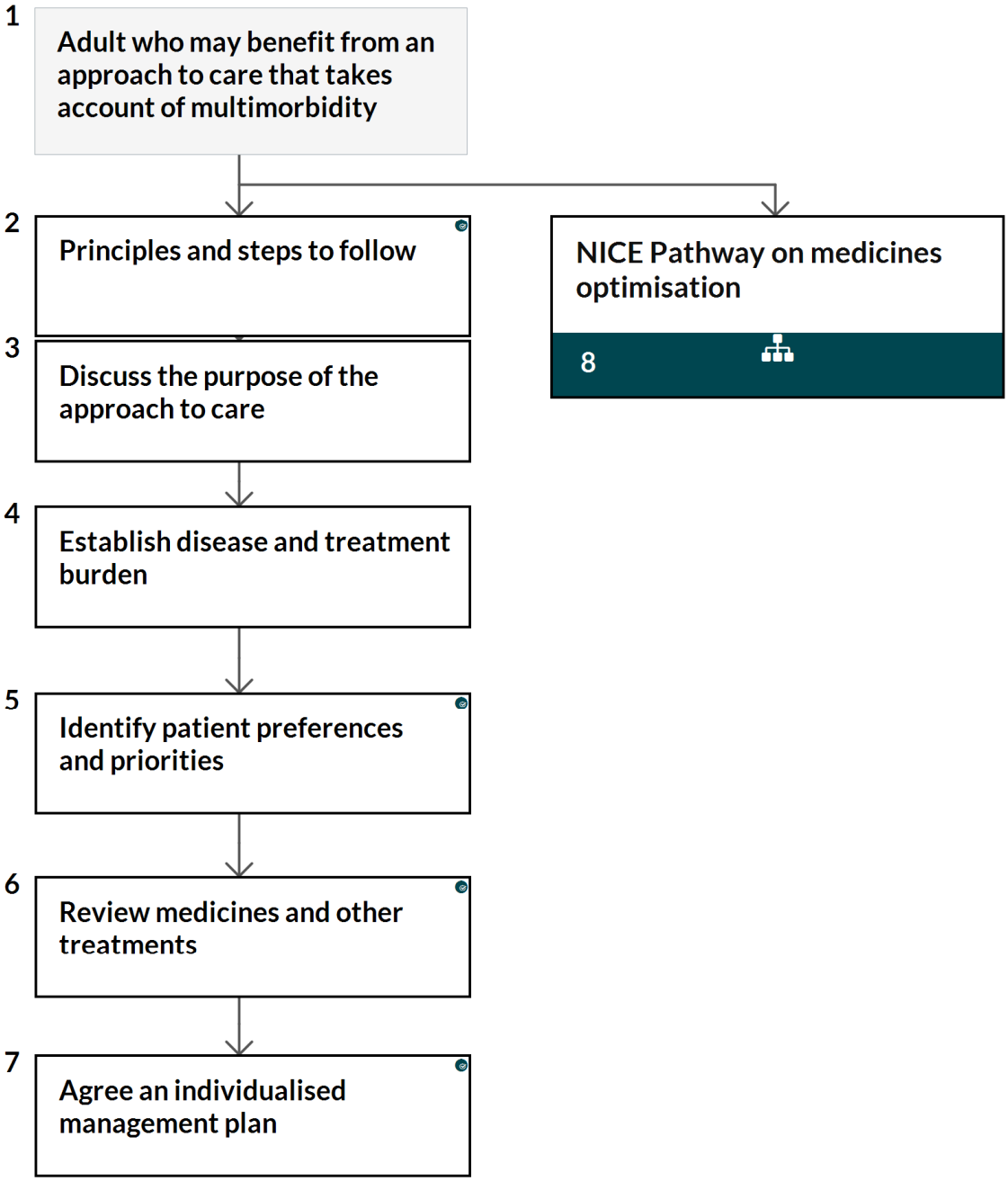


Figure 7.3 NICE pathway on medicines optimisation

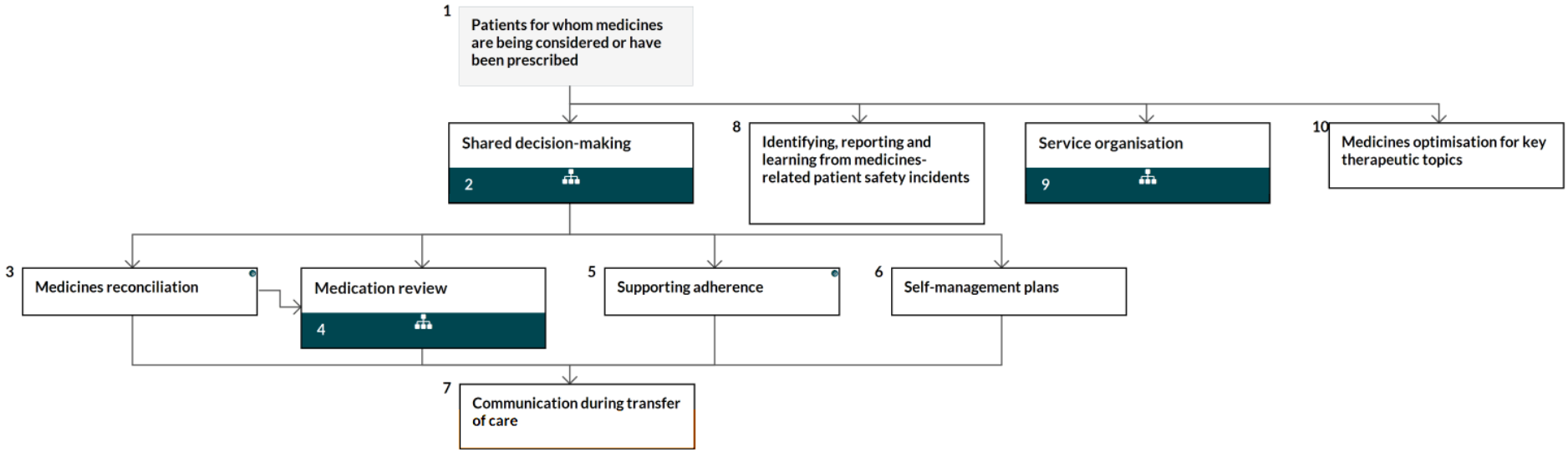
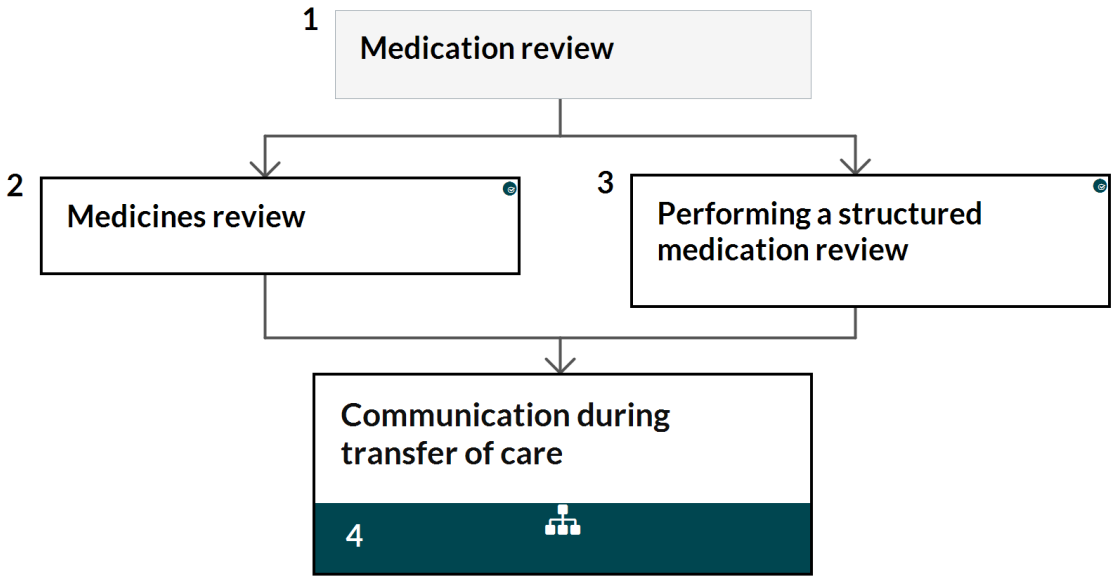


Figure 7.4 NICE interactive flow chart for medication review



The importance of diabetes in the thorough management of multimorbidity and polypharmacy is recognised in this work; nevertheless, an increasing prevalence of both diagnosed and undiagnosed diabetes was found among older adults. Notwithstanding the introduction of public information campaigns (e.g. the UK's annual Diabetes Week) and screening tests in primary care (e.g. NHS Health Checks) to improve diabetes awareness in the population, undiagnosed diabetes has not declined in clinical practice. Only men aged 50–74 showed a stable prevalence of undiagnosed diabetes between 2004 and 2012, with an improved awareness of diabetes; other participants showed a rising prevalence of undiagnosed diabetes. This suggests that men are being identified as at risk more readily than women through the NHS Health Check system, which targets people aged 40−74 years. The findings also suggest that adults aged 75 and over may need regular monitoring of their blood sugar levels to help early diagnosis, as well as the younger targeted population.

In summary, the results of this PhD work suggest that in addition to those with heightened polypharmacy, older adults with polypharmacy should be included in medication reviews. Among this population, those on mental health medications and muscle relaxants are prone to adverse outcomes and therefore may need more attention. This PhD work also highlights the importance of diabetes either in the development of polypharmacy or in adverse outcomes, indicating that older adults with diabetes should be given patient-centred healthcare that takes account of multimorbidity and polypharmacy concurrently. The increasing prevalence of undiagnosed diabetes observed over time further suggests that adults aged 75 and older may need regular monitoring of blood sugar levels to help early diagnosis, in addition to those aged 40−74, who are already targeted. Although polypharmacy is often not negative or inappropriate, early detection could contribute to prompt interventions (i.e. mediation reviews) that would ensure the rationalisation of polypharmacy, decrease medication-related problems, and potentially improve clinical outcomes among community-dwelling older people.

7.4 Research implications

As a longitudinal study of community-dwelling adults aged 50 and over, ELSA has provided an opportunity for researchers to study trends in polypharmacy and its associations with health outcomes since its first collection of medication profiles in 2012. This PhD research established a rigorous definition of polypharmacy in a population-based observational study: two comparable cut-offs (five and 10), medications in long-term use (including OTC drugs), detailed drug inclusion criteria, and counting each distinct pharmacological component as one drug. Although some

combination drugs were not distinguishable from the single drug, and this was acknowledged as a limitation, the proportion was small. This rigorous definition of polypharmacy is a good reference for future studies. Studies where detailed information on medication use is available (i.e. the duration or start/end dates of prescriptions) can employ a clear cut-off of 90 days (three months) in the definition of polypharmacy, instead of using a broad concept of long-term use. In that case, polypharmacy would be defined more rigorously and robustly. This PhD work set up a comprehensive adjustment of comorbidities in observational studies of polypharmacy using specific long-term conditions and an illness count, as a guide for future research. It is recommended that self-reported diagnoses should be verified by medication profiles where possible, and that some conditions should be identified by recognisably specific treatments. The extensive consideration of multimorbidity allows researchers to properly assess the effect of polypharmacy, although observational studies are subject to the residual confounding issue. As ELSA will continue to collect information on medications, researchers will have the opportunity to explore issues related to polypharmacy in more detail over a longer period, using this study as a benchmark.

7.5 Future plans

Several research interests in polypharmacy arise from the research conducted during this PhD. It would be compelling and clinically important to investigate changes in persistent polypharmacy, new polypharmacy, and discontinued polypharmacy between 2012–13 and 2016–18 in this cohort. The change in high-risk medications in the three subgroups could be studied accordingly. Moreover, the role of diabetes in these changes could be investigated. Furthermore, a subgroup analysis of older adults

with limited life expectancy could be explored in terms of the deprescribing situation and alterations in high-risk medications. On the other hand, the association between polypharmacy measured on more than one occasion and mortality could be investigated to see whether sustained polypharmacy better predicts mortality. Lastly, the third collection of medications will be completed in 2022 (Wave 10), and it would be worthwhile to assess the changes in polypharmacy before and after the start of the new structured medication review service in 2020.

In addition to mortality outcomes in this study, depressive symptoms and cognitive impairment showed associations with polypharmacy and interacted with diabetes status; these therefore deserve further investigation. The trajectories of depressive symptoms and cognitive function according to polypharmacy status are well worth studying, especially in relation to diabetes status. Given the importance of quality of life in the literature, studies on the association between polypharmacy and quality of life or life satisfaction could be explored. Furthermore, the linkage between ELSA and hospital episode statistics or electronic health records could provide more information regarding medications and hospital admissions, enabling further studies on inappropriate prescriptions and cause-specific hospitalisations.

7.6 Final conclusion

This PhD consisted of four studies that aimed to examine the prevalence of and risk factors for polypharmacy and its associations with mortality, and the role of diabetes in those relationships. The data came from a nationally representative longitudinal study: ELSA. Taken together, the findings of this work contribute to a better understanding of the role of polypharmacy and diabetes in older adults' health, and

they further highlight the importance of special care for older people with polypharmacy or diabetes. Due to the limitations of this PhD work, more studies are warranted to seek to replicate and expand the present findings, so as to provide more evidence to improve the strategy for polypharmacy management and diabetes care among older adults.

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Appendices

Appendix A Chapter 1 Supplementary tables

Appendix A-1 Diabetes medications and relevant clinical effects*

Drug class	Mechanism	Efficacy	Hypoglycaemia	Weight Change	Cardiovascular‡ Effects		Renal Effects	
					ASCVD‡	CHF‡	DKD progression‡	Avoid use#
Oral								
Biguanide: Metformin	Decrease gluconeogenesis Increase peripheral glucose utilisation Decrease insulin resistance (require presence of insulin)	High	No	Neutral/ loss	Potential benefit	Neutral	Neutral	eGFR‡ < 30
SUs†	Increase insulin secretion (require presence of a functional β-cell mass) Long-term administration: an extrapancreatic action	High	Yes	Gain	Neutral	Neutral	Neutral	Mostly eGFR < 30
Meglitinides	Increase insulin secretion Usually administered premeals: rapid onset, short duration of action	Intermediate	Yes	Gain/ neutral	–	–	–	Dose adjustment required

Appendix A-1 (continued)

Drug class	Mechanism	Efficacy	Hypoglycaemia	Weight Change	Cardiovascular‡ Effects		Renal Effects	
					ASCVD‡	CHF‡	DKD progression‡	Avoid use#
Oral								
α-glucosidase inhibitors: Acarbose**	Delay the digestion and absorption of carbohydrate	Intermediate	No	Neutral	—	—	—	eGFR < 25
TZDs	Reduce peripheral insulin resistance to increase insulin action Stimulate PPARγ‡ Increase adipogenesis Alter glucose-fatty and cycle	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	No dose adjustment required
DPP-4 inhibitors	Increase insulin secretion Lower glucagon secretion Inhibit DPP-4, allowing increased t½ for incretins, which potentiate nutrient-induced insulin secretion	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin, alogliptin	Neutral	Dose adjustment required

Appendix A-1 (continued)

Drug class	Mechanism	Efficacy	Hypoglycaemia	Weight Change	Cardiovascular‡ Effects		Renal Effects	
					ASCVD‡	CHF‡	DKD progression‡	Avoid use#
SGLT-2 inhibitors	Reversibly inhibits SGLT-2 in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, empagliflozin	eGFR < 45; eGFR < 60 in dapagliflozin
Subcutaneous								
Insulin and its analogues	Decrease hepatic glucose production Increase peripheral glucose uptake, storage, and utilisation Decrease lipolysis	Highest	Yes	Gain	Neutral	Neutral	Neutral	Dose adjustment required

Appendix A-1 (continued)

Drug class	Mechanism	Efficacy	Hypoglycaemia	Weight Change	Cardiovascular‡ Effects		Renal Effects	
					ASCVD‡	CHF‡	DKD progression‡	Avoid use#
GLP-1 agonists	Increase insulin secretion Suppress glucagon secretion Slow gastric emptying Resistant to degradation by DPP-4, which potentiate nutrient-induced insulin secretion	High	No	Loss	Benefit: liraglutide; neutral: others	Neutral	Benefit: liraglutide	eGFR < 30

* Three diabetic medications in other classes, Pramlintide (Symlin®), Colesevelam (Cholestagel®) and Bromocriptine, are not included in this table. Pramlintide has been approved to treat diabetes in the USA but it is currently not available in the UK. Colesevelam prescribed in ELSA Wave 6 is all coded as lipid-lowering drugs. Bromocriptine is not approved for diabetic treatment according to the BNF.

† The information here is mainly for second generation of SUs.

** Another α-glucosidase inhibitor, Miglitol, is not included due to unavailability in the UK.

‡ Abbreviations: ASCVD= atherosclerotic cardiovascular disease, CHF= congestive heart failure, DKD= diabetic kidney disease, eGFR= estimated glomerular filtration rate (unit is mL/min/1.73 m^2), PPARγ= peroxisome proliferator-activated receptor gamma.

The information is based on NICE (BNF) and ADA simultaneously.

Appendix B Chapter 3 Supplementary tables

Appendix B-1 Diabetes medications recorded in ELSA

Category	Medications
Insulin	Insulins
Sulfonylureas	Glimepiride, Glibenclamide, Gliclazide, Glipizide, Tolbutamide
Biguanides	Metformin
Meglitinides	Nateglinide, Repaglinide
α-glucosidase inhibitor	Acarbose
TZDs	Pioglitazone, Pioglitazone/metformin
DPP-4 inhibitors	Alogliptin, Alogliptin/metformin, Vildagliptin, Sitagliptin, Sitagliptin/metformin, Saxagliptin, Saxagliptin/metformin, Linagliptin, Linagliptin/metformin
GLP-1 agonists	Exenatide, Liraglutide, Liraglutide/insulin degludec, Lixisenatide
SGLT2 inhibitors	Canagliflozin, Canagliflozin/metformin, Dapagliflozin, Dapagliflozin/metformin, Empagliflozin

Appendix B-2 Undiagnosed diabetes before and after the medication verification in ELSA 2012

	Self-reported	Diagnosed	Undiagnosed
Before verification (N)	890	890	189
After verification (N)	890	930	169

Appendix B-3 Prevalence of diagnosed and undiagnosed diabetes with fasting glucose in England in 2004 and 2012

	2004		2012		Diff.
	%	95% CI	%	95% CI	*P*
Diagnosed diabetes[#]	7.7	7.1, 8.4	11.5	10.7, 12.3	**< 0.001**
Undiagnosed diabetes	1.6	1.2, 2.2	2.0	1.5, 2.8	0.208
Unawareness among diabetic people	18.4	17.5, 19.2	15.7	14.9, 16.5	**< 0.001**

[#] Weighted by non-response weight.

Appendix B-4 Prevalence of diagnosed and undiagnosed diabetes with fasting glucose by age and gender in England in 2004 and 2012

	Age 50-74		Diff.	Age 75+		Diff.
	2004	**2012**	***P***	**2004**	**2012**	***P***
Men						
Diagnosed diabetes[#] %	8.3	11.1	**0.001**	11.7	17.3	**0.002**
95% CI	7.3, 9.4	9.9, 12.4		9.5, 14.3	14.7, 20.3	
Case (N)	234	340		84	141	
Undiagnosed diabetes %	2.0	1.8	0.764	5.2	3.4	0.445
95% CI	1.3, 2.9	1.1, 2.9		2.6, 10.1	1.2, 9.3	
Case (N)	26	22		8	4	
Unawareness among diabetic people %	20.2%	14.7%	**< 0.001**	40.0%	19.2%	**< 0.001**
95% CI	18.7, 21.7	13.3, 16.1		36.4, 43.6	16.5, 21.9	
Women						
Diagnosed diabetes[#] %	5.5	9.2	**< 0.001**	9.7	16.0	**< 0.001**
95% CI	4.7, 6.4	8.1, 10.6		8.0, 11.8	13.7, 18.5	
Case (N)	176	285		98	164	
Undiagnosed diabetes %	1.0	2.2	**0.003**	1.4	0.8	0.55
95% CI	0.5, 1.6	1.4, 3.7		0.3, 5.6	0.2, 3.2	
Case (N)	14	24		2	2	
Unawareness among diabetic people %	14.9%	20.7%	**< 0.001**	14.2%	4.7%	**< 0.001**
95% CI	13.7, 16.1	19.3, 22.1		12.1, 16.3	3.4, 6.0	

[#] Weighted by non-response weight.

Appendix B-5 Prevalence of diagnosed and undiagnosed diabetes with HbA1c of 7% in England in 2004 and 2012

	2004		2012		Diff.
	%	95% CI	%	95% CI	*P*
Diagnosed diabetes[#]	7.7	7.1, 8.4	11.5	10.7, 12.3	**< 0.001**
Undiagnosed diabetes	1.0	0.7, 1.3	1.3	1.0, 1.8	0.076
Unawareness among diabetic people	11.3	10.6, 12.0	10.2	9.6, 10.9	**0.039**

[#] Weighted by non-response weight.

Appendix B-6 Prevalence of diagnosed and undiagnosed diabetes with HbA1c of 7% by age and gender in England in 2004 and 2012

	Age 50-74		Diff.	Age 75+		Diff.
	2004	**2012**	***P***	**2004**	**2012**	***P***
Men						
Diagnosed diabetes[#] %	8.3	11.1	**0.001**	11.7	17.3	**0.002**
95% CI	7.3, 9.4	9.9, 12.4		9.5, 14.3	14.7, 20.3	
Case (N)	234	340		84	141	
Undiagnosed diabetes %	1.7	0.9	**0.031**	1.4	3.0	0.084
95% CI	1.2, 2.4	0.5, 1.6		0.6, 3.3	1.6, 5.6	
Case (N)	29	15		6	11	
Unawareness among diabetic people %	16.7%	7.4%	**< 0.001**	11.3%	15.6%	**0.014**
95% CI	15.3, 18.1	6.4, 8.4		9.0, 13.6	13.1, 18.1	
Women						
Diagnosed diabetes[#] %	5.5	9.2	**< 0.001**	9.7	16.0	**< 0.001**
95% CI	4.7, 6.4	8.1, 10.6		8.0, 11.8	13.7, 18.5	
Case (N)	176	285		98	164	
Undiagnosed diabetes %	0.4	1.6	**< 0.001**	0.6	0.8	0.739
95% CI	0.2, 0.9	1.0, 2.5		0.2, 1.6	0.3, 1.9	
Case (N)	8	27		4	5	
Unawareness among diabetic people %	6.8%	14.4%	**< 0.001**	6.1%	4.4%	0.080
95% CI	5.9, 7.7	13.2, 15.6		4.6, 7.6	3.2, 5.6	

[#] Weighted by non-response weight.

Appendix B-7 Prevalence of diagnosed and undiagnosed diabetes in the same individuals in England in 2004 and 2012

	2004		2012	
	%	95% CI	%	95% CI
Diagnosed diabetes[#]	6.2	5.5, 7.0	13.8	12.7, 14.9
Undiagnosed diabetes	1.9	1.4, 2.5	4.0	3.2, 5.0
Unawareness among diabetic people	23.8	22.9, 24.8	23.2	22.3, 24.1

[#] Weighted by non-response weight.

Appendix B-8 Longitudinal prevalence of diagnosed and undiagnosed diabetes in the same individuals by age and gender in England in 2004 and 2012

	Age 50-74		Age 75+	
	2004	**2012**	**2004**	**2012**
Men (N)	1675	1233	220	662
Diagnosed diabetes[#] %	7.3	15.6	8.6	16.7
95% CI	6.2, 8.7	13.5, 17.9	5.5, 13.3	13.9, 20.0
Case (N)	126	186	19	108
Undiagnosed diabetes %	2.7	2.3	1.7	6.5
95% CI	1.9, 3.8	1.4, 3.8	0.5, 5.2	4.1, 10.2
Case (N)	30	16	3	20
Unawareness among diabetic people %	27.5	12.6	16.3	31.7
95% CI	25.4, 29.6	10.7, 14.5	11.4, 21.2	28.2, 35.2
Women (N)	2113	1533	322	902
Diagnosed diabetes[#] %	4.8	9.1	7.7	16.1
95% CI	3.9, 5.8	7.7, 10.8	5.2, 11.1	13.7, 18.9
Case (N)	103	133	26	137
Undiagnosed diabetes %	1.5	4.0	0.7	4.4
95% CI	0.9, 2.4	2.7, 5.8	0.2, 2.7	2.7, 7.2
Case (N)	20	37	2	20
Unawareness among diabetic people %	24.3	32.4	7.9	22.6
95% CI	22.5, 26.1	30.1, 34.7	5.0, 10.8	19.9, 25.3

[#] Weighted by non-response weight.

Appendix B-9 Cohort characteristics in people without diabetes based on HbA1c availability in ELSA 2012

	No missing (N = 5206) % (N)	**Missing (N = 1593) % (N)**	***P***
Age (years) mean ± SD	66.6 ± 9.1	69.6 ± 10.3	**< 0.001**
Gender			
Men	44.1 (2298)	41.9 (668)	0.120
Women	55.9 (2908)	58.1 (925)	
Education			
No qualifications	22.0 (1141)	28.5 (452)	**< 0.001**
Some qualifications	78.0 (4041)	71.6 (1137)	
Ethnicity			
White	97.6 (5083)	96.5 (1537)	**0.012**
Non-white	2.4 (123)	3.5 (56)	
Living with a partner	70.2 (3654)	64.1 (1021)	**< 0.001**
Total wealth			
1 (lowest)	18.1 (884)	22.9 (342)	**< 0.001**
2	19.2 (940)	20.1 (301)	
3	20.3 (993)	19.9 (298)	
4	21.1 (1031)	18.9 (282)	
5 (highest)	21.4 (1050)	18.2 (272)	
Social class based on occupation			
Professional-managerial or intermediate	63.8 (3287)	58.7 (922)	**< 0.001**
Manual	36.2 (1864)	41.3 (649)	
Obesity			
High BMI and waist circumference	25.9 (1297)	31.3 (451)	**< 0.001**
Either high BMI or high waist circumference	23.3 (1166)	24.3 (350)	
SBP (mmHg) mean ± SD	132.2 ± 17.4	131.4 ± 18.4	0.147
DBP (mmHg) mean ± SD	74.5 ± 10.5	72.3 ± 10.9	**< 0.001**
Triglyceride (mmol/L) mean ± SD	1.5 ± 0.8	1.4 ± 0.6	0.304
Cholesterol (mmol/L) mean ± SD	5.7 ± 1.1	5.7 ± 1.2	0.777

Appendix B-9 (continued)

	No missing (N = 5206) % (N)	**Missing (N = 1593) % (N)**	***P***
Current smoker	11.4 (594)	11.6 (184)	0.877
Cognitive function mean ± SD	11.1 ± 3.5	10.2 ± 3.8	**< 0.001**
Hypertension	34.9 (1815)	41.7 (664)	**< 0.001**
CVD	18.8 (976)	33.3 (530)	**< 0.001**
Hyperlipidaemia	35.3 (1840)	37.0 (589)	0.235
CES-D scores			
Less than 4	88.8 (4588)	84.2 (1325)	**< 0.001**
4 and above	11.2 (577)	15.8 (249)	

Appendix B-10 Prevalence of diagnosed diabetes between 2003 and 2012 from the Health Survey for England[*]

Year	2003	2006	2009	2010	2011[#]	2012
Overall (%)	3.9	4.9	5.5	5.8	5.9	5.8
Age groups (years)						
16-24	0.6	0.9	0.4	0.4	0.7	0.5
25-44	1.4	1.5	1.8	2.0	1.9	1.3
45-64	4.6	6.0	7.0	7.4	7.5	7.8
65+	9.7	12.3	13.8	13.9	14.4	14.4

[*] Data are from the website of the Health Survey for England, and the years not given are unavailable.

[#] HbA1c-based diagnosis was applied in the UK.

Appendix C Chapter 4 Supplementary tables

Appendix C-1 Prevalence of medications presumably not in long-term use in ELSA 2012, stratified by diabetes

Medication category	No diabetes (N = 6629) N (%)	Diabetes (N = 1100) N (%)	Total (N = 7729) N (%)
Pain relief − paracetamol-based	872 (13.2)	257 (23.4)*	1129 (14.6)
Gastrointestinal symptoms (except for peptic ulcers)	177 (2.7)	50 (4.6)*	227 (2.9)
Constipation	225 (3.4)	56 (5.1)*	281 (3.6)
Allergy and vertigo (antihistamine)	206 (3.1)	53 (4.8)*	259 (3.4)
Cough	12 (0.2)	2 (0.2)	14 (0.2)
Nausea and vertigo	110 (1.7)	35 (3.2)*	145 (1.9)
Infection	215 (3.2)	52 (4.7)*	267 (3.5)
Supplements (except for those for bone disease)	405 (6.1)	130 (11.8)*	535 (6.9)

* Significantly higher proportions in people with diabetes.

Appendix C-2 Prevalence of polypharmacy in ELSA 2012

		Number of drugs			
		0	**1−4**	**5−9***	**10+***
All long-term drugs	N	2093	3752	1656	228
	%	31.1	46.5	19.6	2.8
	95% CI	29.8, 32.4	45.2, 47.8	18.7, 20.7	2.5, 3.3
Long-term drugs excluding	N	2109	3882	1563	175
antihyperglycemic drugs	%	31.2	48.1	18.4	2.2
	95% CI	29.9, 32.6	46.8, 49.5	17.5, 19.4	1.9, 2.6

* Five to nine drugs was defined as polypharmacy; 10+ was defined as heightened polypharmacy.

Appendix C-3 Risk factors for polypharmacy in people without diabetes (N = 5372) with an adjustment for specific conditions, ELSA 2012

	Polypharmacy (N = 806)			Heightened polypharmacy (N = 72)		
	RRR*	95% CI	*P*	RRR*	95% CI	*P*
Age	1.04	1.02, 1.05	**< 0.001**	1.01	0.97, 1.04	0.648
Female sex	0.81	0.66, 0.98	**0.035**	0.70	0.40, 1.22	0.210
Non-white ethnicity	0.72	0.34, 1.55	0.404	2.43	0.60, 9.85	0.215
Total wealth						
2nd	0.88	0.66, 1.17	0.393	1.32	0.64, 2.76	0.453
3rd	0.77	0.58, 1.04	0.091	0.90	0.41, 2.01	0.803
4th	0.99	0.73, 1.36	0.971	1.21	0.50, 2.96	0.669
5th quintile (richest)	0.65	0.46, 0.92	**0.015**	0.90	0.34, 2.41	0.836
No educational qualifications	1.13	0.90, 1.41	0.309	1.03	0.57, 1.89	0.916
Manual social class	1.01	0.82, 1.24	0.943	0.91	0.51, 1.61	0.734
Living with a partner	1.41	1.13, 1.76	**0.003**	1.07	0.60, 1.93	0.812
Number of CVD	3.52	3.02, 4.10	**< 0.001**	5.96	4.31, 8.24	**< 0.001**
Hypertension	3.13	2.58, 3.80	**< 0.001**	2.80	1.61, 4.85	**< 0.001**
Hyperlipidaemia	1.80	1.49, 2.17	**< 0.001**	2.31	1.35, 3.97	**0.002**
Psychiatric conditions	2.07	1.63, 2.63	**< 0.001**	3.27	1.86, 5.77	**< 0.001**
Number of conditions#	2.21	2.00, 2.43	**< 0.001**	3.90	3.06, 4.98	**< 0.001**
Current smoker	1.81	1.31, 2.50	**< 0.001**	1.90	0.82, 4.41	0.136
Alcohol consumption: daily (5−7 days per week)	1.14	0.91, 1.43	0.249	0.87	0.44, 1.75	0.705
Obesity§						
High BMI and waist circumference	1.67	1.33, 2.08	**< 0.001**	1.18	0.63, 2.22	0.598
Either high BMI or high waist circumference	1.17	0.93, 1.48	0.179	1.09	0.58, 2.05	0.790
Cognitive function	0.96	0.93, 0.98	**0.003**	0.89	0.82, 0.97	**0.006**
Number of depressive symptoms	1.09	1.03, 1.15	**0.002**	1.15	1.02, 1.30	**0.024**

* Unweighted RRR.

The rest of other conditions, not including diabetes.

§ Normal BMI and waist circumference as the reference group.

Appendix C-4 Risk factors for polypharmacy in people with diabetes (N = 783) with an adjustment for specific conditions, ELSA 2012

	Polypharmacy (N = 397)			Heightened polypharmacy (N = 66)		
	RRR*	95% CI	*P*	RRR*	95% CI	*P*
Age	1.01	0.99, 1.04	0.313	0.98	0.93, 1.02	0.315
Female sex	0.50	0.34, 0.73	**< 0.001**	0.50	0.24, 1.01	**0.053**†
Non-white ethnicity	1.05	0.48, 2.27	0.910	0.97	0.21, 4.51	0.968
Total wealth						
2nd	0.97	0.58, 1.63	0.918	1.41	0.54, 3.68	0.480
3rd	0.79	0.47, 1.33	0.374	1.88	0.70, 5.03	0.207
4th	1.29	0.72, 2.33	0.396	1.19	0.32, 4.37	0.795
5th quintile (richest)	0.60	0.32, 1.12	0.107	1.40	0.39, 4.98	0.605
No educational qualifications	1.06	0.69, 1.63	0.776	0.99	0.45, 2.15	0.976
Manual social class	1.43	0.98, 2.10	0.066	1.75	0.85, 3.61	0.130
Living with a partner	0.96	0.65, 1.43	0.850	1.01	0.49, 2.10	0.969
Number of CVD	2.19	1.62, 2.96	**< 0.001**	3.54	2.20, 5.70	**< 0.001**
Hypertension	2.39	1.67, 3.43	**< 0.001**	3.79	1.64, 8.78	**0.002**
Hyperlipidaemia	1.52	1.07, 2.14	**0.019**	1.59	0.78, 3.27	0.205
Psychiatric conditions	4.35	2.54, 7.46	**< 0.001**	6.35	2.81, 14.33	**< 0.001**
Number of conditions#	1.56	1.28, 1.91	**< 0.001**	3.88	2.76, 5.45	**< 0.001**
Current smoker	1.28	0.72, 2.27	0.402	1.28	0.45, 3.66	0.641
Alcohol consumption: daily (5−7 days per week)	0.89	0.55, 1.46	0.648	0.55	0.18, 1.66	0.291
Obesity§						
High BMI and waist circumference	1.70	1.11, 2.62	**0.015**	3.58	1.26, 10.15	**0.016**
Either high BMI or high waist circumference	1.13	0.70, 1.82	0.621	2.00	0.63, 6.38	0.239
Cognitive function	1.00	0.95, 1.06	0.988	0.96	0.86, 1.06	0.421
Number of depressive symptoms	1.06	0.95, 1.18	0.316	1.24	1.05, 1.47	**0.012**

* Unweighted RRR.

The rest of other conditions, not including diabetes.

† Borderline significant.

§ Normal BMI and waist circumference as the reference group.

Appendix C-5 Prevalence of long-term conditions, according to polypharmacy and diabetes status

	No diabetes (N = 6629)		Diabetes (N = 1100)	
	No polypharmacy (N = 5424) % (N)	Polypharmacy* (N = 1205) % (N)	No polypharmacy (N = 421) % (N)	Polypharmacy* (N = 679) % (N)
Number of conditions# mean ± SD	1.8 ±1.4	4.2 ±1.6	2.3 ± 1.4	4.2 ± 1.8
CVD	14.6% (789)	55.2% (665)	19.2% (81)	49.3% (335)
Hypertension	29.3% (1591)	65.6% (791)	51.5% (217)	74.5% (506)
Hyperlipidaemia	30.8% (1668)	56.9% (685)	46.8% (197)	65.5% (445)
Psychiatric conditions	14.2% (771)	30.0% (362)	8.8% (37)	29.9% (203)
Lung diseases (including asthma)	12.3% (665)	36.0% (434)	11.4% (48)	26.2% (178)

Not including diabetes.

* Including polypharmacy and heightened polypharmacy.

Appendix D Chapter 5 Supplementary tables and figures

Appendix D-1 Questions in assessments of ADLs, IADLs and mobility

Assessment	Question
ADL	Difficulty dressing, including putting on shoes and socks
	Difficulty walking across a room
	Difficulty bathing or showering
	Difficulty eating, such as cutting up food
	Difficulty getting in and out of bed
	Difficulty using the toilet, including getting up or down
IADL	Difficulty using map to figure out how to get around strange place
	Difficulty recognising when in physical danger
	Difficulty preparing a hot meal
	Difficulty shopping for groceries
	Difficulty making telephone calls
	Difficulty with communication (speech, hearing or eyesight)
	Difficulty taking medications
	Difficulty doing work around house and garden
	Difficulty managing money, eg paying bills, keeping track expenses
Mobility	Difficulty walking 100 yards
	Difficulty sitting 2 hours
	Difficulty getting up from chair after sitting long periods
	Difficulty climbing several flights stairs without resting
	Difficulty climbing one flight stairs without resting
	Difficulty stooping, kneeling or crouching
	Difficulty reaching or extending arms above shoulder level
	Difficulty pulling or pushing large objects
	Difficulty lifting or carrying weights over 10 pounds
	Difficulty picking up 5p coin from table
All questions are recorded as binary variables: Not mentioned vs Mentioned	

Appendix D-2 Significant factors associated with all-cause mortality from the fully adjusted model in England 2012−18

	HR (95% CIs)	*P*
Number of concurrent drugs (Ref=none)		
Polypharmacy (5−9 drugs)	1.51 (1.05, 2.16)	**0.026**
Heightened polypharmacy (10+ drugs)	2.29 (1.40, 3.75)	**0.001**
Age (years)[#]	1.11 (1.10, 1.12)	**< 0.001**
Gender (Ref=men)	0.60 (0.49, 0.72)	**< 0.001**
Living with a partner (Ref=no)	0.75 (0.61, 0.92)	**0.006**
Diabetes mellitus (Ref=no)	1.28 (1.02, 1.60)	**0.035**
CHD (Ref=no)	1.28 (1.02, 1.60)	**0.030**
Lung disease (including asthma) (Ref=no)	1.28 (1.03, 1.60)	**0.028**
Obesity (Ref=normal BMI and waist circumference)		
High BMI and waist circumference	0.70 (0.55, 0.88)	**0.003**
Either high BMI or high waist circumference	0.76 (0.61, 0.95)	**0.015**
Current smoker (Ref=no)	1.89 (1.44, 2.49)	**< 0.001**
Low physical activity (Ref=moderate/high)	1.54 (1.25, 1.89)	**< 0.001**
Cognitive function[#]	0.95 (0.92, 0.97)	**< 0.001**

[#] Per one-unit increase.

Appendix D-3 Sensitivity analyses of the associations between number of concurrent drugs and all-cause mortality in England 2012−18

	None	1−4 drugs		5−9 drugs*		10+ drugs*	
N = 6295 (499 deaths)	HR	HR (95% CIs)	*P*	HR (95% CIs)	*P*	HR (95% CIs)	*P*
SA1. Main model + drug-disease interactions	1.00 (Ref)	1.09 (0.79, 1.48)	0.603	1.50 (1.04, 2.15)	**0.028**	2.25 (1.37, 3.70)	**0.001**
SA2. Main model + alcohol consumption#	1.00 (Ref)	1.15 (0.82, 1.61)	0.414	1.57 (1.06, 2.33)	**0.025**	2.08 (1.19, 3.65)	**0.011**
SA3. Main model + taking medications but without diagnoses§	1.00 (Ref)	1.13 (0.82, 1.55)	0.458	1.60 (1.10, 2.34)	**0.015**	2.47 (1.48, 4.13)	**0.001**
SA4. Main model with multimorbidity†	1.00 (Ref)	1.19 (0.86, 1.65)	0.299	1.86 (1.30, 2.67)	**0.001**	3.19 (2.02, 5.06)	**< 0.001**
SA5. Main model with all long-term conditions††	1.00 (Ref)	1.14 (0.83, 1.56)	0.425	1.53 (1.06, 2.20)	**0.023**	2.16 (1.31, 3.56)	**0.003**

* Polypharmacy refers to taking five to nine drugs; heightened polypharmacy refers to taking 10 or more drugs.

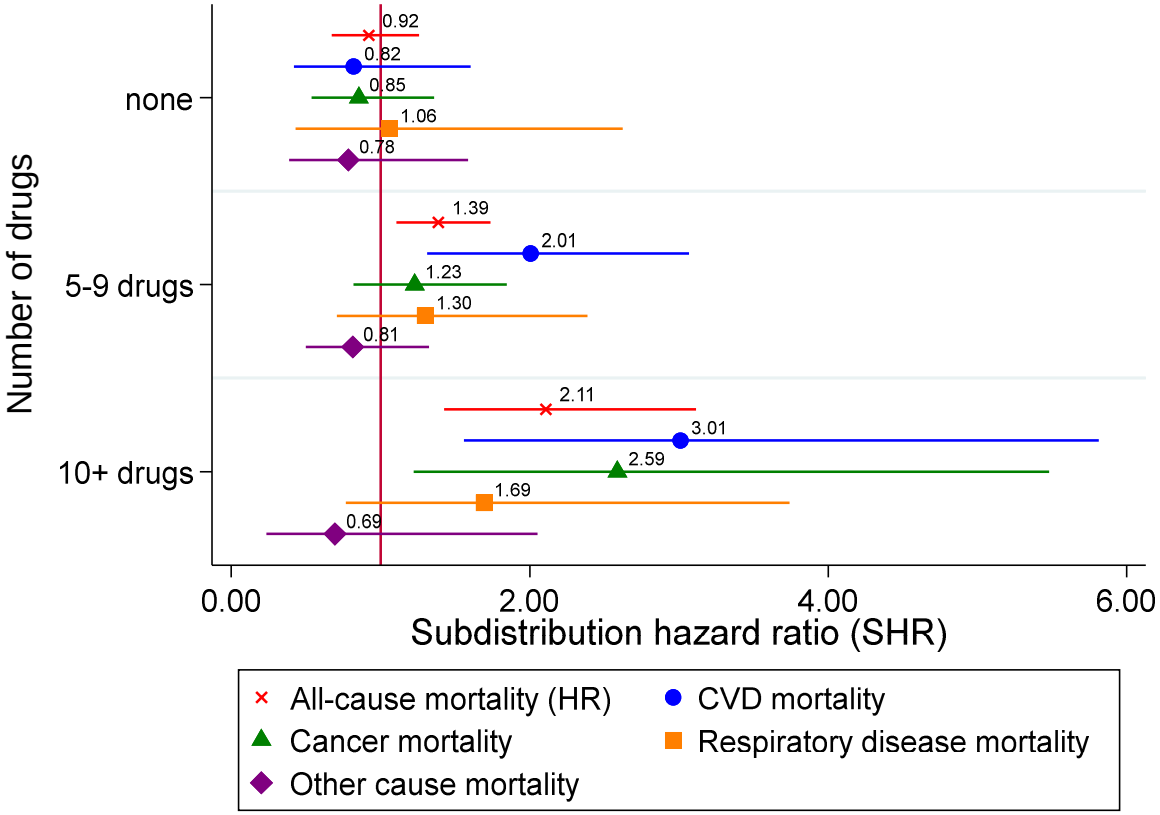
Reduced N = 5805 (429 deaths).

§ A small proportion of people who took medications but did not report relevant diagnoses.

† Replace particular long-term conditions and the illness count with multimorbidity, defined as the coexistence of two or more long-term conditions.

†† Replace the number of conditions with separate diagnoses, including hypertension, other heart problems, hyperlipidaemia, arthritis, bone disease, psychiatric conditions, eye disease, gout or hyperuricemia, epilepsy, and inflammatory bowel disease.

Appendix D-4 The sixth sensitivity analysis: associations[#] between number of concurrent drugs and all-cause and cause-specific mortality with 1−4 drugs as the reference in England in 2012−18



[#] Adjusted for age, gender, cohabitation, wealth, six long-term conditions (diabetes, CHD, stroke, lung disease, Parkinson's disease, and dementia), an illness count of the remaining conditions, functional impairment, mobility difficulty, obesity, smoking status, sleep duration, low physical activity, cognitive function, and depressive symptoms.

Appendix E Chapter 6 Supplementary tables

Appendix E-1 Additional baseline characteristics† of people with polypharmacy (N = 1356) by cluster, ELSA 2012

	Cluster 1 RAAS inhibitors (N = 194) % (N)	Cluster 2 Mental health drugs (N = 298) % (N)	Cluster 3 CNS drugs (N = 387) % (N)	Cluster 4 RAAS inhibitors + antithrombotics (N = 352) % (N)	Cluster 5 Antithrombotics (N = 125) % (N)
Total wealth					
1 (lowest)	26.3 (51)	34.6 (103)	29.7 (115)	24.2 (85)	30.4 (38)
2	22.2 (43)	24.8 (74)	23.5 (91)	21.0 (74)	23.2 (29)
3	22.2 (43)	19.5 (58)	17.3 (67)	21.6 (76)	18.4 (23)
4	16.0 (31)	13.1 (39)	19.4 (75)	19.3 (68)	20.0 (25)
5 (highest)	13.4 (26)	8.1 (24)	10.1 (39)	13.9 (49)	8.0 (10)
Parkinson's disease	0	0.7 (2)	5.2 (20)	0	0.8 (1)
Dementia (including Alzheimer's disease)	1.0 (2)	3.4 (10)	3.4 (13)	0.3 (1)	0.8 (1)
Cognitive function mean (SD)	10.0 (3.2)	9.4 (3.6)	9.7 (3.7)	9.8 (3.2)	9.3 (3.7)

† Including two variables (total wealth and cognitive function) with similar distributions across the five clusters and two conditions (Parkinson's disease and dementia (including Alzheimer's disease)) with low prevalence rates.

Appendix E-2 Sensitivity analyses of the associations between medication patterns[*] and mortality in people with polypharmacy in England in 2012−18

All-cause mortality, N = 1356 (235 deaths)	Cluster 1 RAAS inhibitors		Cluster 2 Mental health drugs		Cluster 4 RAAS inhibitors + antithrombotics		Cluster 5 Antithrombotics	
	HR (95% CIs)	P	HR (95% CIs)	P	HR (95% CIs)	P	HR (95% CIs)	P
Main model	1.56 (0.97, 2.50)	0.064	1.55 (1.05, 2.28)	**0.028**	1.17 (0.78, 1.76)	0.454	1.43 (0.89, 2.30)	0.140
SA1. Main model with separate CVD conditions[‖]	1.56 (0.97, 2.51)	0.068	1.53 (1.03, 2.26)	**0.033**	1.12 (0.74, 1.70)	0.597	1.41 (0.88, 2.27)	0.156
SA2. Main model with separate psychiatric conditions	1.57 (0.97, 2.52)	0.065	1.54 (1.02, 2.32)	**0.041**	1.17 (0.78, 1.77)	0.450	1.43 (0.89, 2.31)	0.140
SA3. Main model + alcohol consumption[#]	1.56 (0.93, 2.64)	0.094	1.70 (1.10, 2.63)	**0.017**	1.13 (0.72, 1.78)	0.582	1.37 (0.81, 2.33)	0.237
SA4. Main model + taking medications but without diagnoses[§]	1.56 (0.97, 2.50)	0.064	1.54 (1.04, 2.29)	**0.030**	1.17 (0.78, 1.75)	0.455	1.43 (0.89, 2.30)	0.142

Appendix E-2 (continued)

CVD mortality, N = 1356 (96 deaths)	Cluster 1 RAAS inhibitors		Cluster 2 Mental health drugs		Cluster 4 RAAS inhibitors + antithrombotics		Cluster 5 Antithrombotics	
	SHR (95% CIs)	P	SHR (95% CIs)	P	SHR (95% CIs)	P	SHR (95% CIs)	P
Main model	1.26 (0.55, 2.91)	0.583	2.11 (1.10, 4.05)	**0.024**	1.49 (0.76, 2.89)	0.243	1.17 (0.50, 2.76)	0.721
SA1. Main model with separate CVD conditions‖	1.27 (0.55, 2.97)	0.578	2.10 (1.09, 4.04)	**0.027**	1.43 (0.72, 2.84)	0.301	1.16 (0.49, 2.73)	0.739
SA2. Main model with separate psychiatric conditions	1.25 (0.54, 2.91)	0.598	2.13 (1.07, 4.27)	**0.032**	1.48 (0.75, 2.92)	0.262	1.16 (0.49, 2.75)	0.730
SA3. Main model + alcohol consumption#	1.95 (0.76, 5.04)	0.166	3.04 (1.42, 6.52)	**0.004**	1.83 (0.82, 4.08)	0.139	1.36 (0.49, 3.72)	0.554
SA4. Main model + taking medications but without diagnoses§	1.27 (0.55, 2.92)	0.571	2.03 (1.04, 3.95)	**0.038**	1.49 (0.77, 2.87)	0.239	1.14 (0.48, 2.70)	0.762
SA5. Main model using Cox regression†	1.40 (0.60, 3.25)	0.437	2.16 (1.14, 4.09)	**0.018**	1.44 (0.75, 2.76)	0.278	1.41 (0.62, 3.18)	0.413

Appendix E-2 (continued)

Non-CVD mortality, N = 1356 (139 deaths)	Cluster 1 RAAS inhibitors		Cluster 2 Mental health drugs		Cluster 4 RAAS inhibitors + antithrombotics		Cluster 5 Antithrombotics	
	SHR (95% CIs)	P	SHR (95% CIs)	P	SHR (95% CIs)	P	SHR (95% CIs)	P
Main model	1.48 (0.80, 2.73)	0.214	1.18 (0.72, 1.94)	0.518	0.93 (0.55, 1.57)	0.774	1.49 (0.82, 2.70)	0.189
SA1. Main model with separate CVD conditions‖	1.47 (0.80, 2.71)	0.218	1.17 (0.71, 1.92)	0.541	0.90 (0.52, 1.53)	0.691	1.47 (0.82, 2.66)	0.196
SA2. Main model with separate psychiatric conditions	1.50 (0.80, 2.79)	0.206	1.15 (0.68, 1.96)	0.598	0.94 (0.55, 1.59)	0.812	1.51 (0.83, 2.74)	0.179
SA3. Main model + alcohol consumption#	1.36 (0.72, 2.58)	0.344	1.03 (0.59, 1.82)	0.914	0.77 (0.43, 1.38)	0.383	1.28 (0.65, 2.53)	0.474
SA4. Main model + taking medications but without diagnoses§	1.47 (0.80, 2.72)	0.218	1.19 (0.72, 1.98)	0.493	0.93 (0.55, 1.57)	0.775	1.50 (0.82, 2.73)	0.186
SA5. Main model using Cox regression††	1.76 (1.00, 3.11)	0.052	1.35 (0.82, 2.23)	0.240	1.01 (0.59, 1.72)	0.970	1.62 (0.90, 2.91)	0.106

* Cluster 3 CNS drugs (N = 387) as the reference group.

‖ Four cardiovascular-related diagnoses − CHD, stroke, hypertension, and other heart problems − were adjusted separately instead of combining some diagnoses into an illness count.

Reduced N = 1221 (195 all-cause deaths; 82 CVD deaths; 113 non-CVD deaths).

Appendix E-2 (continued)

[§] A small proportion of people who took medications but did not report relevant diagnoses.

[†] Cox regression was used rather than competing-risks regression, and non-CVD deaths were recoded as missing values. N = 1217 (96 deaths).

[††] Cox regression was used rather than competing-risks regression, and CVD deaths were recoded as missing values. N = 1260 (139 deaths).